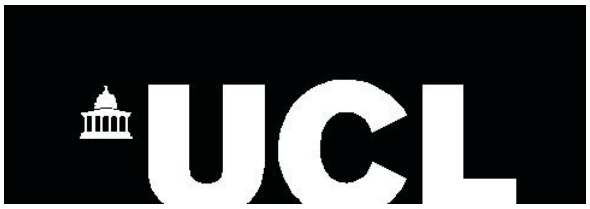
Development of an Enantioselective Reductive Nitro-Mannich Reaction using Thiourea Catalysis



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I, Paul John Koovits confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

The introductory chapter of this thesis describes in detail the chemistry of the nitro-Mannich reaction from its inception to the current "state of the art". Additionally, the products of the nitro-Mannich reaction and their uses in synthesis are also discussed. The final section of the introduction deals with the use of thiourea organocatalysis and its application in synthetic transformations using imines or nitroalkenes as electrophiles.

The results and discussion initially focuses on the development of a racemic reductive nitro-Mannich reaction. It has been found that when using Superhydride^{TM} as a hydride source, a variety of nitroalkenes underwent selective reduction. The corresponding nitronates formed then underwent an *in situ* nitro-Mannich reaction upon addition of an *N*-*para*-methoxy phenyl (PMP) protected imine and trifluoroacetic acid to form *β*-nitroamines in excellent conversion (>90%) and high diastereoselectivities (75:25 to >95:5 *dr*). These products were then protected by reaction with trifluoroacetic anhydride and pyridine, to enable isolation of the products as trifluoroacetamides in good to excellent yields (58-87%) and diastereoselectivity (>90:10 *dr*). The second part details the development of an enantioselective variant using thiourea organocatalysis. It was discovered that the desired reductive nitro-Mannich reaction could be promoted with excellent levels of stereocontrol using a Hantzsch ester as the hydride source and a simple thiourea catalyst derived from *L*-valine. The reaction worked well for a variety of different nitroalkenes and *N*-PMP protected imines using toluene as a solvent at -20 ^{o}C. The resultant products could be isolated after protection as trifluoroacetamides in moderate to excellent yields (32-84%), high diastereoselectivity (>90:10 *dr*) and good to excellent enantioselectivity (73-99% *ee*). The final part of this chapter discusses progress towards the synthesis of 1,2-diamine containing natural product Eudistomidin B, using a reductive nitro-Mannich reaction as the key step.

The conclusions of the research and potential future work are also presented along with analytical data. Detailed preparative methods for all compounds synthesised in this research are also described. Finally an appendix section is included, which contains a list of abbreviations, a table of coupling constants and a comprehensive list of references.

Acknowledgements

First of all I'd like to thank Jim for letting me work on this project and his support throughout my time researching in his group. He will probably be the best boss I will ever have and in particular I'll miss the interesting discussions regarding chemistry as well as the sometimes bizarre anecdotes from the world of academia.

I'd also like to thank all of the members of the Anderson group, past and present, for their help during the past few years and more importantly for the compulsary coffee breaks; pub lunches; and the various outings ranging from roller disco, to a night at the zoo, that have helped to keep me sane. The KLB guys should also get a mention here for frequent ulu drinks on Friday.

Additionally I want to thank all of the UCL technical staff for all their help and for the NMR, mass spec. and elemental analysis data.

Thanks to the various flatmates that I've had the pleasure to live with over the past three years. Everyone has been excellent and I owe you all a lot of gratitude for giving me lots of memories and fun times outside of the lab. Also thanks to the Fairbridge lot in particular for letting me stay on the sofa so often over the past few months.

Finally, I'd like to thank my family and close friends for all their support and encouragement over the years and putting up with my occassional moping and despair when things weren't going well.

So with that there's just one thing left to do (the pint of ice cold cava). Oh and there's the small matter of a *viva* as well.

Cheers everyone

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Chapter 1. Introduction

1.1 The nitro-Mannich reaction

1.1.1 Overview

The formation of new carbon-carbon bonds represents some of the most fundamental reactions available to synthetic chemists. The addition of an active C-H nucleophile to a C=X π bond represents a simple and atom efficient carbon-carbon bond forming reaction. Within this widely utilised family of reactions are the famous aldol reaction,[1] and its aza-equivalents: the Mannich,[2] Henry (or aza-aldol)[3] and the nitro-Mannich (or aza-Henry)[4] reactions (Figure 1).

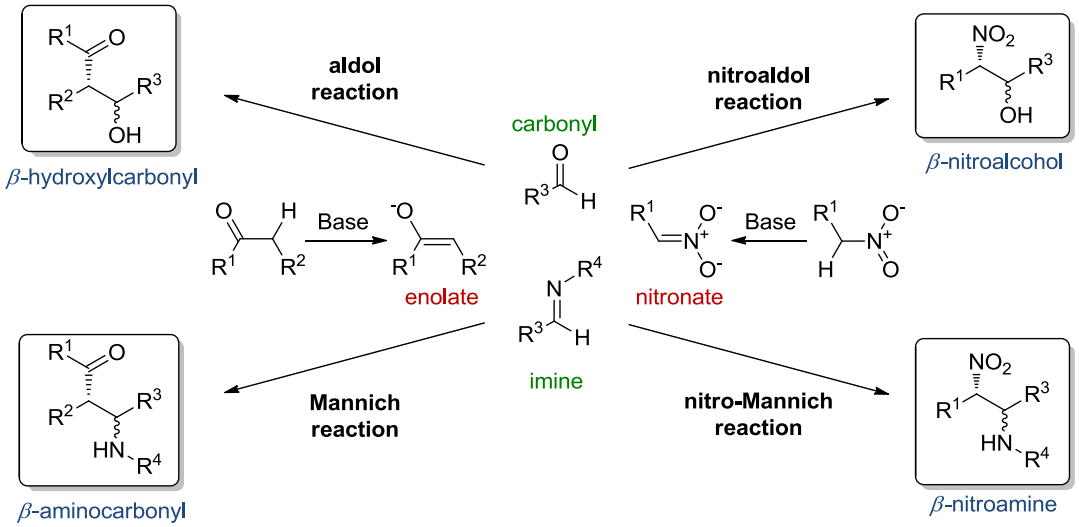


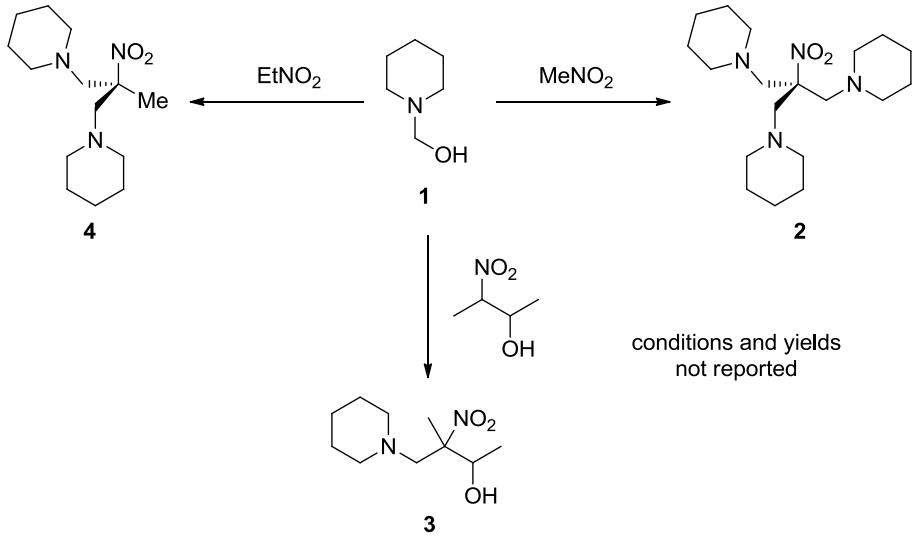
Figure 1. The aldol, nitroaldol, Mannich and nitro-Mannich reactions

Whilst the enolate-based aldol and Mannich reactions have been extensively studied, the nitro-Mannich and Henry reactions, which react *via* a nitronate species, have been much less well researched. The *β*-nitroamine products possess two nitrogens in different oxidation states which allows for complete chemoselectivity in subsequent transformations. Despite the high potential of the nitro-Mannich reaction products, the reaction had received little attention up until 1998 when the Anderson group published the first efficient diastereoselective procedure.[5] Since that seminal publication, there has been much more research performed in this field. This has led to the discovery of several protocols utilising organometallic and organocatalysts to deliver both the common *anti* and the rarer *syn* diastereomers with high levels of enantioselectivity. There have been several small reviews on the nitro-Mannich

reaction.[6] As such, the remainder of this section will discuss a brief history of the nitro-Mannich reaction and will try to focus on some of the more pivotal publications in greater detail.

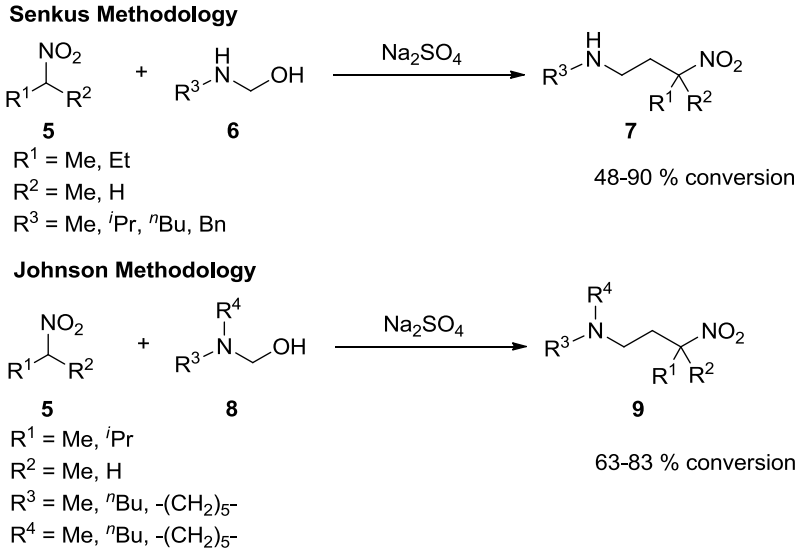
1.1.2 Discovery and developments pre-1998

The first nitro-Mannich (or aza-Henry) reaction was reported in 1896 by Henry.[4] It was disclosed that a variety of nitroalkanes would add to hemiaminal **1** to form *β*-nitroamines (Scheme 1). The exact conditions were never reported but it is assumed that loss of a water molecule from the hemiaminal to give an imimium ion followed by attack from the nitronate occurs. Very similar results to this were reported a few years later by Mousset using nitroisobutane and hemiaminal **1** but the exact conditions were once more not reported.[7]



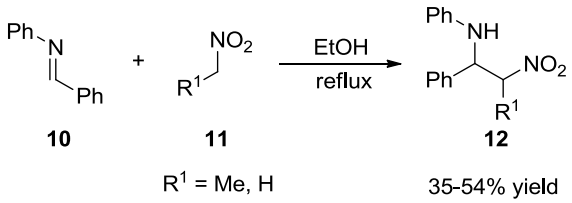
Scheme 1. The first reported nitro-Mannich reaction

The next major development came in the mid-20th century when Senkus and Johnson simultaneously published more detailed accounts of the nitro-Mannich reaction (Scheme 2).[8] Senkus was able to report moderate to good conversion to *β*-nitroamine products **7** when using hemiaminals **6**, formed from primary amines. Johnson described a similar protocol using hemiaminals **8** formed from secondary amines and formaldehyde.



Scheme 2. Senkus's and Johnson's nitro-Mannich procedures

Another notable report of a nitro-Mannich reaction prior to 1998 was the publication of the first nitro-Mannich reaction using pre-formed imine **10** with nitroethane or nitromethane in refluxing ethanol by the group of Hurd. However, these reactions only proceeded with moderate yields and the authors did not comment on the diastereoselectivity (Scheme 3).[9]



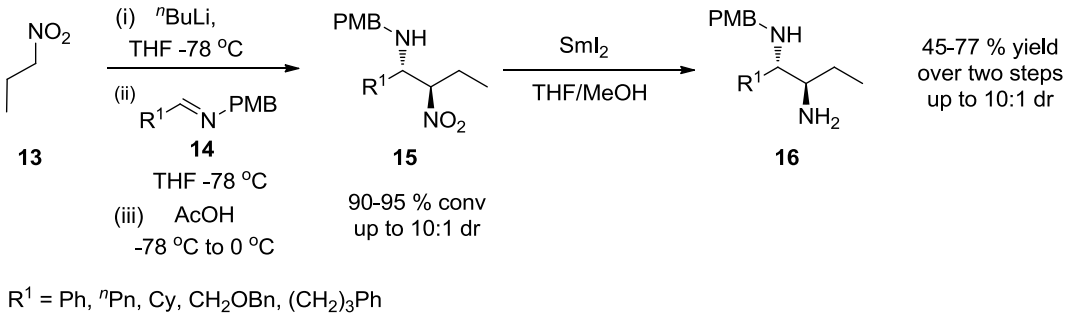
Scheme 3. The first nitro-Mannich reaction using a pre-formed imine

As well as the reactions described thus far there were some other examples of early nitro-Mannich reactions pre-1998 but they are less noteworthy in regards to this work. [10]

1.1.3 Non-catalytic coupling

It was over 100 years from the nitro-Mannich reaction's discovery to the development of the first acyclic diastereoselective nitro-Mannich reaction by the Anderson group in 1998.[5] The authors reported that the direct addition of lithium nitronates, formed from nitroethane **13**, to *para*-methoxy benzyl (PMB) protected imines **14** in the presence of acetic acid gave the desired *β*-nitroamines **15** diastereomerically enriched as the *anti* diastereomer (Scheme 4). The acetic acid was required in the reaction to

activate the imine. Without activation using a Brønsted acid there is no reaction observed.

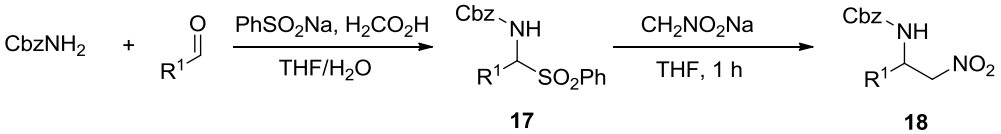


R^1 = Ph, ^{n}Pn, Cy, CH_2OBn, $(CH_2)_3Ph$

Scheme 4. First acyclic diastereoselective nitro-Mannich reaction

The *β*-nitroamine products **15** were unstable to standard purification techniques and as such had to be reduced to vicinal diamines using samarium diiodide to calculate an isolated yield. This instability of *β*-nitroamines is a recurrent problem with the nitro-Mannich reaction, especially if there is no electron withdrawing group on the amine. The products frequently have to be immediately reacted to prevent degradation of the *β*-nitroamine *via* a retro nitro-Mannich reaction.

One year later, Petrini *et al.* reported the base assisted reaction between *α*-amidoalkyl sulfones **17** and sodium methanenitronate (Scheme 5).[11] It was proposed that the excess of the sodium methanenitronate species (formed from nitromethane and sodium hydride) can eliminate phenyl sulfinic acid from *α*-amidoalkyl sulfone **17** and form an acyl imine species *in situ*. This imine can then react with the remainder of the sodium methanenitronate *via* a nitro-Mannich reaction to form *β*-nitroamines **18** in high yields.

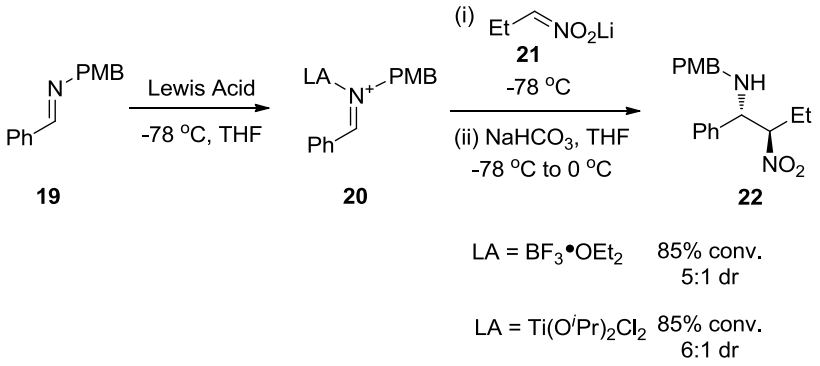


R^1 = Et, Cy, $Ph(CH_2)_2$, $Cl(CH_2)_5$, $NO_2(CH_2)_5$, $BnO(CH_2)_4$

Scheme 5. Base-assisted nitro-Mannich reaction of *α*-amidoalkyl sulfones

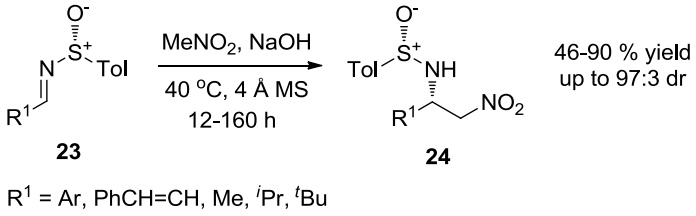
The Anderson group have also reported another diastereoselective non-catalytic nitro-Mannich reaction using Lewis acids.[12] Using $BF_3{\cdot}OEt_2$ or $Ti(O^iPr)_2Cl_2$ as a Lewis acid to activate PMB-imines **19**, the nitro-Mannich reaction could be promoted when added to pre-formed lithium nitronate **21** (Scheme 6). The reaction gave good

conversions but the scope was not explored as the authors were seeking to develop a catalytic method which was later achieved using silyl nitronates (see section 1.1.4).



Scheme 6. Lewis acid promoted nitro-Mannich reaction

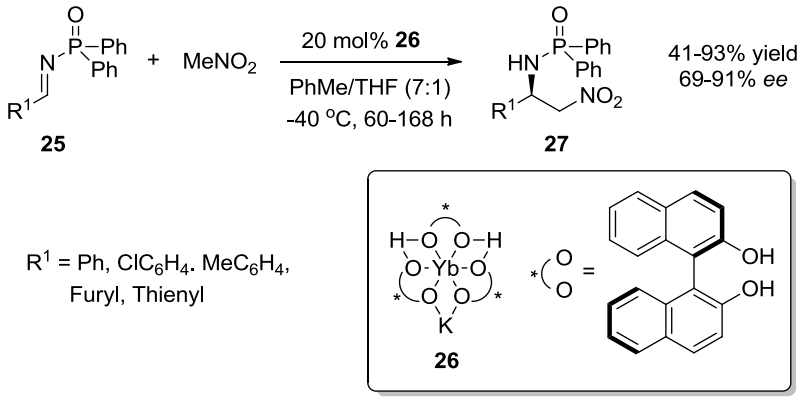
There have also been several chiral auxiliary controlled nitro-Mannich reactions reported.[13] Ruano and Cid *et al.* reported the first auxiliary controlled nitro-Mannich reaction in 2005 (Scheme 7).[14] Using *para*-tolylsulfinyl imines **23**, desired *β*-nitroamines **24** were synthesised in moderate to good yields and with good to excellent diastereoselectivity. The authors were also able to promote the reaction using TBAF (tetrabutylammonium fluoride) instead of sodium hydroxide, however the diastereoselectivity was significantly lower.



Scheme 7. Chiral auxiliary controlled nitro-Mannich reaction

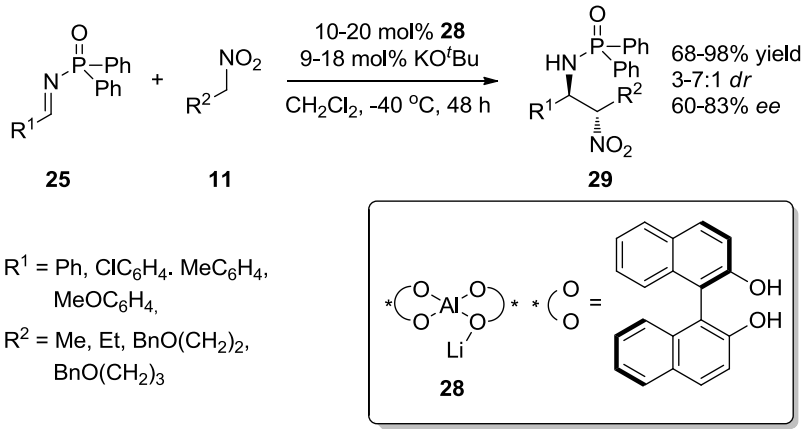
1.1.4 Metal catalysed reactions

Shibasaki and co-workers reported the first catalytic enantioselective nitro-Mannich reaction in 1999 using phosphonate protected imines **25,** nitromethane and chiral Yb/K/BINAP catalyst **26**, which acted as both a Lewis acid and Brønsted base (Scheme 8).[15] The main drawbacks of the reaction were the long reaction times and that the catalyst could only promote the nitro-Mannich reaction with nitromethane.



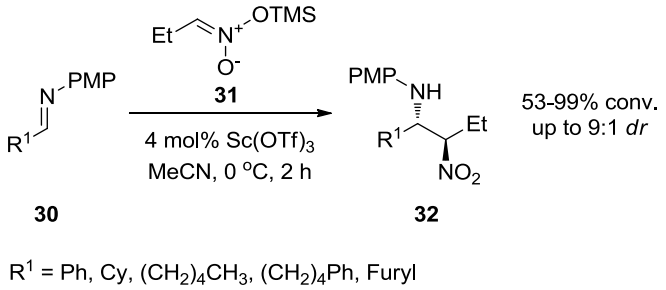
Scheme 8. First catalytic enantioselective nitro-Mannich reaction

An improved catalytic system was later published by the Shibasaki group that overcame the limitations of the previous work to become the first diastereoselective and enantioselective nitro-Mannich reaction (Scheme 9).[16] Although some of the limitations of the previous publication have been dealt with, the new catalyst system was unable to furnish the products with as high a level of enantioselectivity as those with simpler nitroalkane precursors.



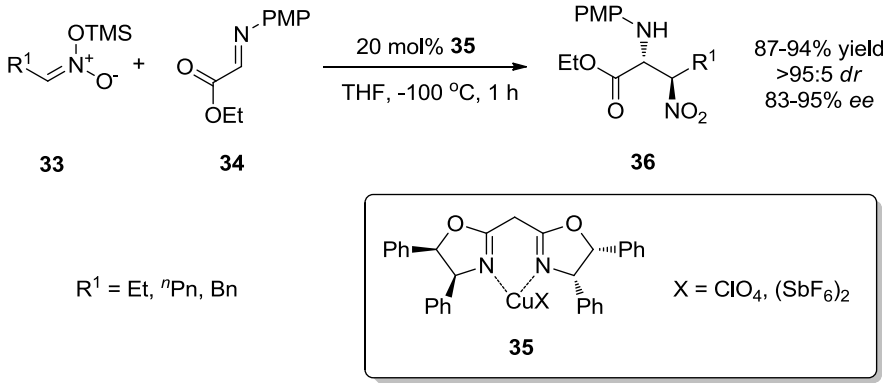
Scheme 9. First diastereo- and enantioselective nitro-Mannich reaction

In between the two reports by Shibasaki *et al.* the Anderson group published a nitro-Mannich reaction of silyl nitronate **31** with *para*-methoxy phenyl (PMP) imines **30** promoted by a catalytic quantity of $Sc(OTf)_3$ (Scheme 10).[12] The reactions had initially been attempted with PMB-imines, as used in previous work, but the diastereoselectivity was poor. Altering the protecting group to PMP gave much better diastereomeric ratios. The scope of the reaction was reported in greater detail in 2004 when $Cu(OTf)_2$ and $Ti(O^iPr)_4$ were also shown to be effective catalysts for the reaction and an *ortho*-methoxy benzyl (OMB) group was used as the protecting group.[17]



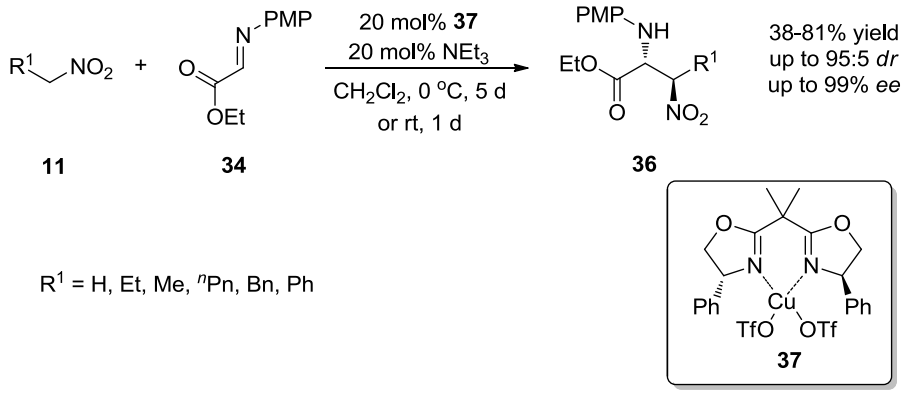
Scheme 10. Lewis acid catalysed nitro-Mannich reaction

Jørgensen *et al.* reported the first asymmetric nitro-Mannich reaction of silyl-nitronates **33** with PMP-*α*-imino esters **34** to give optically active *β*-nitro-*α*-amino esters **36** using a chiral copper catalyst (Scheme 11).[18] The products were formed with high enantio- and diastereoselectivity when reactions were performed at -100 °C but the scope of the reaction was limited to imino esters.



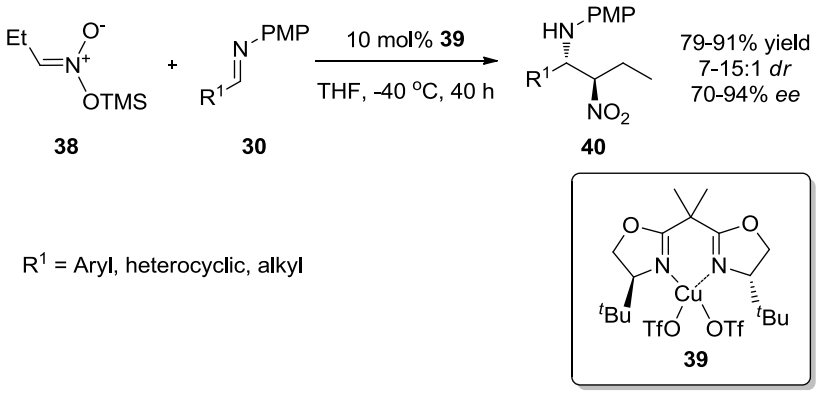
Scheme 11. First asymmetric nitro-Mannich reaction using silyl-nitronates

The same group also published an alternative strategy using simple nitroalkanes **11** instead of silyl-nitronates (Scheme 12).[19] This reaction required the use of an organic base to deprotonate the nitroalkane as well as chiral copper catalyst **37**. Unlike the reaction depicted in scheme 11, the reaction temperatures used were much easier to achieve although the reaction times were also much longer. Later, the group of Hyeon immobilized this catalyst onto a silica support to create a recyclable catalyst system.[20] Although successful, the new catalyst was less selective and upon recycling the levels of stereoselectivity further decreased.



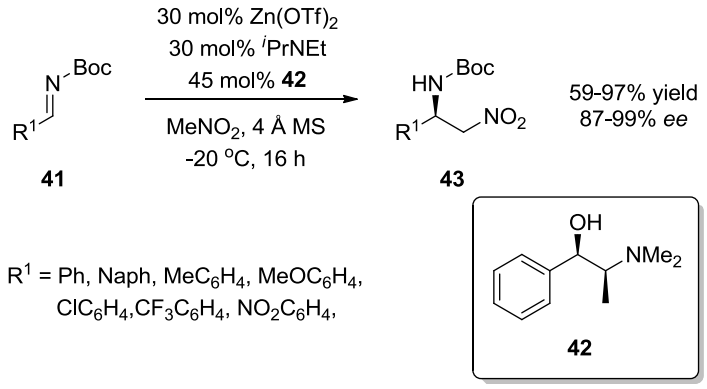
Scheme 12. Enantioselective nitro-Mannich reaction of PMP-*α*-imino esters

In 2005, encouraged by their own research,[17] and the publication by Jørgensen *et al.*[18] the Anderson group reported the catalytic enantioselective nitro-Mannich reaction of silyl-nitronate **38** with PMP-protected imines **30** giving *anti β*-nitroamines **40** in good yields and selectivity (Scheme 13).[21] The authors used a chiral ^{t}Bu-BOX ligand and copper (II) metal as the Lewis acid catalyst.



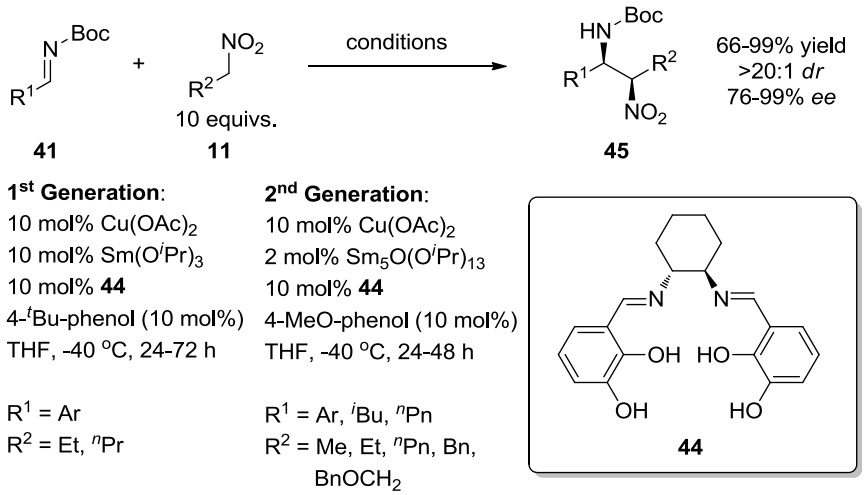
Scheme 13. Asymmetric nitro-Mannich reaction of TMS-nitronates

In the following year, Palomo and co-workers reported an enantioselective nitro-Mannich reaction using zinc (II) catalysis.[22] The authors used (-)-*N*-methylephedrine (NME) **42** as the chiral ligand and a tertiary amine as base to produce the desired products **43** in good yield and enantioselectivity. However, the reaction used large amounts of ligand (45 mol%) and nitromethane was used as solvent. The groups of Qian and Trost have also published Zn catalysed nitro-Mannich reactions.[23] These reactions use a dinuclear zinc complex and are significantly more efficient, requiring 5 and 2 equivalents of nitromethane respectively.



Scheme 14. Zn (II) catalysed asymmetric nitro-Mannich reaction

So far only *anti* selective reactions have been discussed; the development of a *syn*-selective metal catalysed nitro-Mannich reaction was not published until 2007. Shibasaki's group reported the use of heterobimetallic Cu/Sm/Schiff base complex with Schiff base **44** as the catalyst in a *syn*-selective nitro-Mannich reaction (Scheme 15, 1st generation).[24] The reaction achieved excellent selectivity, was high yielding and works well for a large range of substrates. The 4-^{t}Bu-phenol additive was crucial for the very high enantioselectivity (80 *vs.* 94% *ee* in screening). It was proposed to be involved as a ligand and not as a simple proton source as the use of hindered 2,6-(^{t}Bu)2-phenol had no beneficial effect on enantioselectivity. The only limitation of the catalyst system was that imines with alkyl groups such as ^{n}pentyl or *iso*-butyl gave poor enantioselectivity. More recently, a much more detailed report of this *syn*-selective nitro-Mannich reaction complete with ESI-MS analysis of the catalyst structure has been disclosed.[25]



Scheme 15. First metal-catalysed *syn*-selective nitro-Mannich reaction

As a result of this report it was discovered that 4-MeO-phenol and $Sm_5O(O^iPr)_{13}$ gave the best enantioselectivity and allowed catalyst loadings as low as 1 mol% for some reactions. The new catalyst system also overcame the previous limitations and an expanded scope for the reaction was shown (Scheme 15, 2nd generation). However, the reaction is still limited by the large excess of nitroalkane **11** (10 equiv.) required. A possible transition state was also proposed to explain the unusual *syn*-selectivity through cooperative dual activation of the nitroalkane by Sm and the imine by Cu. Of the plausible transition states (Figure 2), **TS-1** has less unfavourable steric clashes and as such is favoured over **TS-2**.

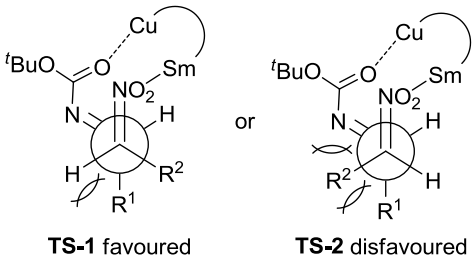
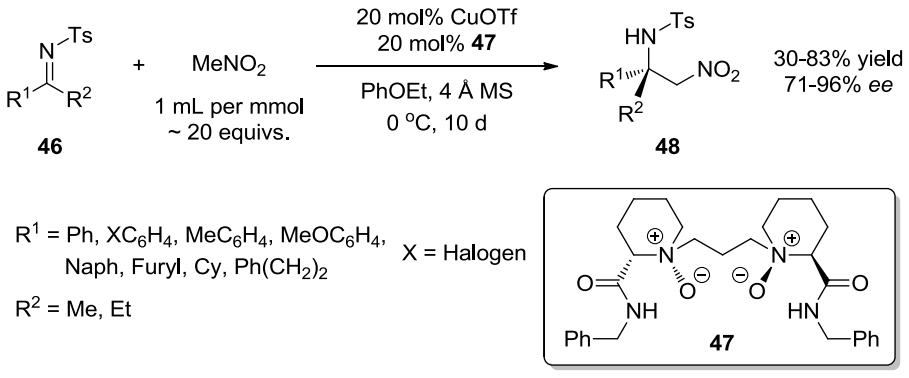


Figure 2. Proposed transition states for *syn*-selective nitro-Mannich reaction

In 2008, Feng *et al.* reported the first enantioselective nitro-Mannich reaction of ketimines **46** (Scheme 16).[26] Using a combination of copper (I) triflate and *N,N'*,-dioxide ligand **47** in phenyl ethyl ether the authors were able to react nitromethane with a variety ketimines in moderate to good yields and high levels of enantioselectivity. Unfortunately, the rate of reaction was very slow, taking 10 days to reach acceptable yields and used approximately 20 equivalents of nitromethane.



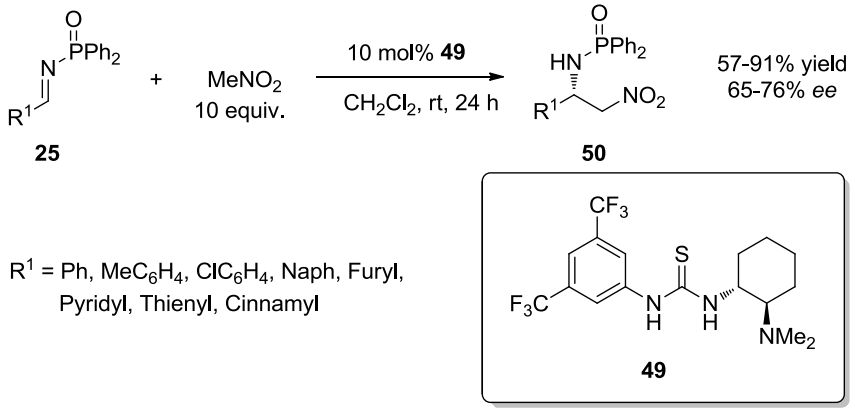
Scheme 16. First enantioselective nitro-Mannich reaction of ketimines

Although there have been other reports of metal-catalysed nitro-Mannich protocols, the reactions currently described in this section represent the state-of-the-art for this

particular aspect of nitro-Mannich chemistry and as such the remainder of this section shall discuss the use of non-metallic catalytic systems.

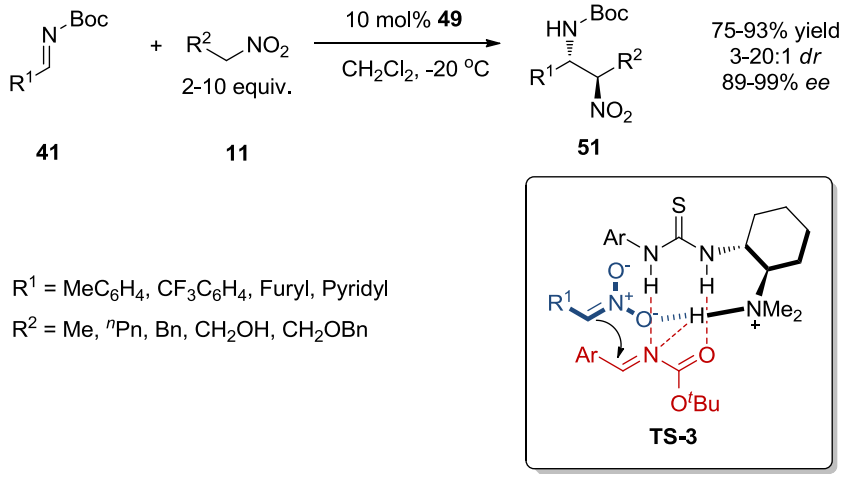
1.1.5 Organocatalytic nitro-Mannich reactions

Despite the first enantioselective organocatalysed reactions having been described in the early 1970s,[27] the field of organocatalysis lay dormant for almost 30 years after. Since the late 1990s however, thanks to the seminal publications by a few research groups,[28] the field has exploded with research and nowadays many reactions can be performed asymmetrically using organocatalysis. The nitro-Mannich reaction is no exception and has been shown to proceed asymmetrically using a variety of organocatalysts. The first organocatalytic nitro-Mannich reaction was reported by Takemoto *et al*. in 2004.[29] Using thiourea catalyst **49**, good yields and moderate to good enantioselectivities could be achieved for the nitro-Mannich reaction between nitromethane and a variety of phosphinoylimines **25** (Scheme 17).



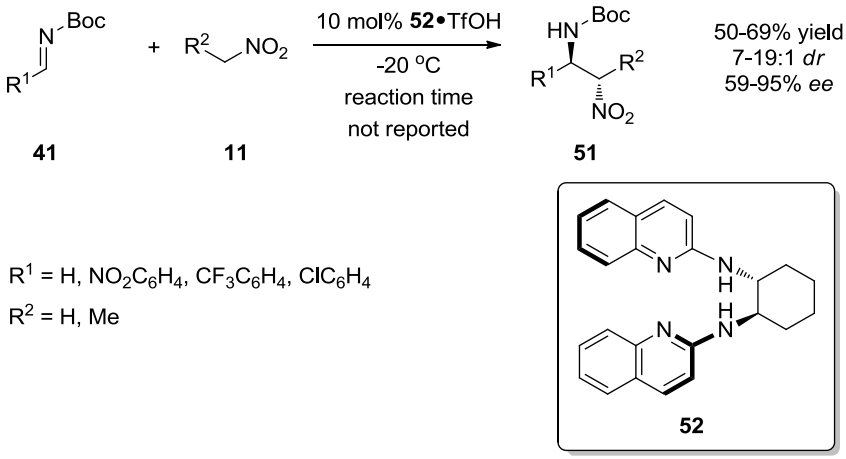
Scheme 17. First organocatalytic nitro-Mannich reaction

More details on this organocatalysed reaction were published by the Takemoto group two years later.[30] This paper described how the enantioselectivities of the reaction could be greatly improved by using *N*-Boc-imines **41** and lowering the temperature to -20 ^{o}C.



Scheme 18. Thiourea catalysed nitro-Mannich reaction of *N*-Boc imines

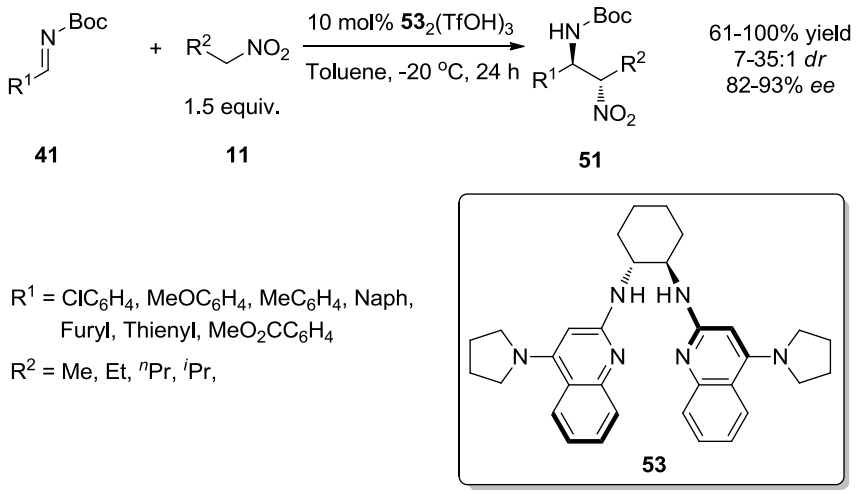
It was also showed that under these conditions the reaction could be performed with various other nitroalkanes **11** to give desired products **51** with moderate to high diastereoselectivity and excellent enantioselectivity. The authors also proposed a mechanism with **TS-3** as the transition state. In **TS-3**, both the imine and the nitroalkane are activated by the thiourea group and the acidic Me_2NH^+ group. Almost simultaneous to the original Takemoto publication in 2004, Johnston *et al.* disclosed the use of Brønsted acid catalysis to promote the nitro-Mannich reaction.[31] Using the triflate salt of chiral bisamidine (BAM) **52** the authors were able to promote the reaction of *N*-Boc imines **41** bearing electron withdrawing groups with nitromethane or nitroethane as solvent to give desired *β*-nitroamines **51** in moderate to good yields and in some cases excellent enantioselectivity (Scheme 19).



Scheme 19. Chiral bisamidine Brønsted acid catalysed nitro-Mannich reaction

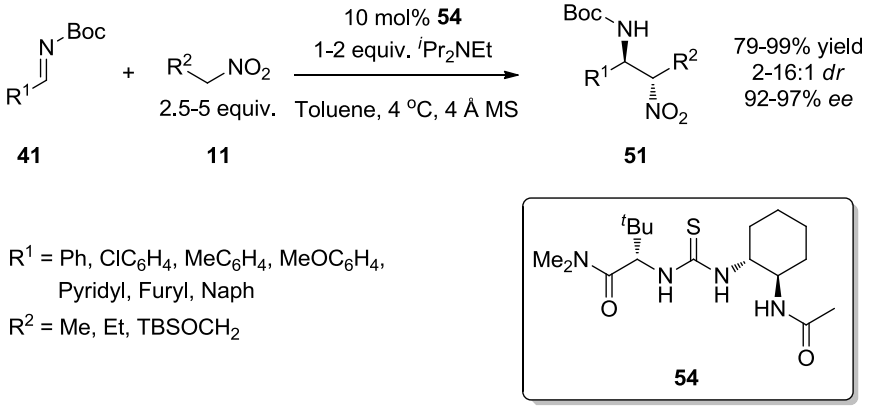
Recently, Johnston's group have reported a greatly improved procedure using a combination of BAM ligand **53** and triflic acid (Scheme 20).[32] It was observed that

the use of the mono-triflate salt of BAM **53** gave a great a drastic improvement in the rate of reaction when using nitroethane (complete reaction 24 h with 1.5 equiv. $EtNO_2$) in comparison to the mono-triflate salt of **52** (<5 % conversion in 24 h) used in the previous work (Scheme 19). This is reasoned to be due to the increased basicity of **53** resulting from the pyrrolidine groups in the 4-position of the quinolones. Interestingly, the ratio of triflic acid to BAM **53** was found to be crucial and a ratio of 3:2 was found to be the optimum mixture.



Scheme 20. Improved Brønsted acid catalysed nitro-Mannich reaction

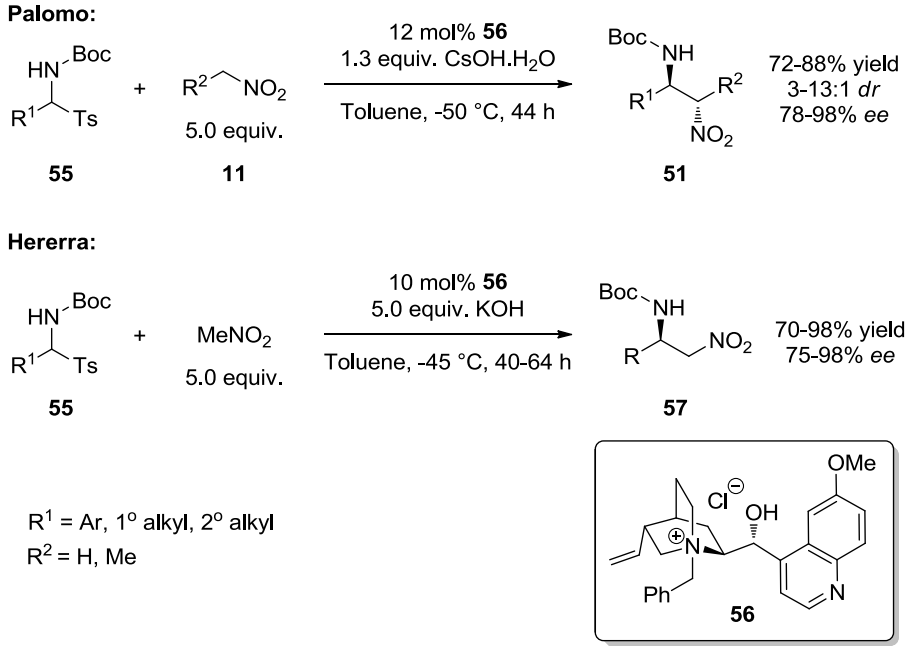
In 2005, Jacobsen *et al.*[33] described a stereoselective nitro-Mannich reaction of nitroalkanes **11** to a variety of *N*-Boc Imines **41** using thiourea catalyst **54** and an external organic base (Scheme 21). The reaction gave the desired products in high yields with good diastereoselectivity and excellent enantioselectivity in most cases.



Scheme 21. Thiourea catalysed nitro-Mannich reaction

Shortly after, the groups of Palomo and Herrera independently reported the first phase-transfer catalysed asymmetric nitro-Mannich reactions (Scheme 22).[34] Their

procedures were very similar and only differed in the choice of inorganic base. Palomo's group also tested nitroethane in the reaction to produce diastereomeric products with modest to excellent selectivity.



Scheme 22. Phase-transfer catalysed nitro-Mannich reactions

Palomo *et al.* later published a more detailed report of their phase-transfer system, complete with experimental and theoretical studies.[35] After extensive computational calculations the group proposed that the nitro group, rather than the imine, H-bonds to the OH group of the catalyst (bond B in Figure 3). An intramolecular H-bond in the catalyst was also observed between this oxygen and a C-H bond on the quinoline ring (bond A). From this they computed a variety of possible transition states and found that when the imine is attacked from the *Si* face **(TS-4**) the resulting transition state had the lowest possible energy (Figure 3), predicting the observed stereochemistry. In **TS-4**, the Boc-amide of the imine is tightly bound to the catalyst by three H-bonds (C, D and E) and both the *tert*-butyl and phenyl groups of the imine are placed in non-sterically demanding positions. The authors suggest that contrastingly when the nitronate attacks from the *Re* face (**TS-5**), giving the opposite enantiomer, the *tert*-butyl group is pointed towards the bicycle of the catalyst. This may explain the increase in energy for this transition state.

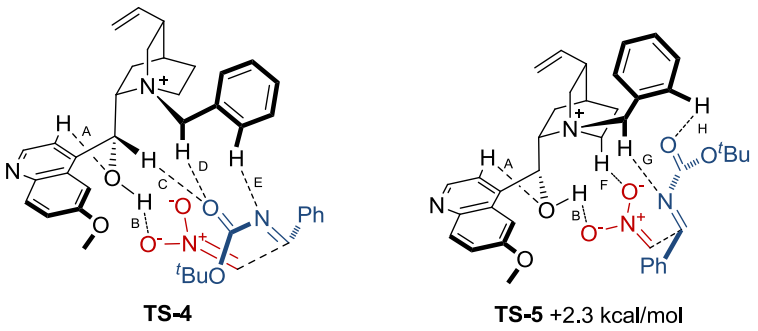
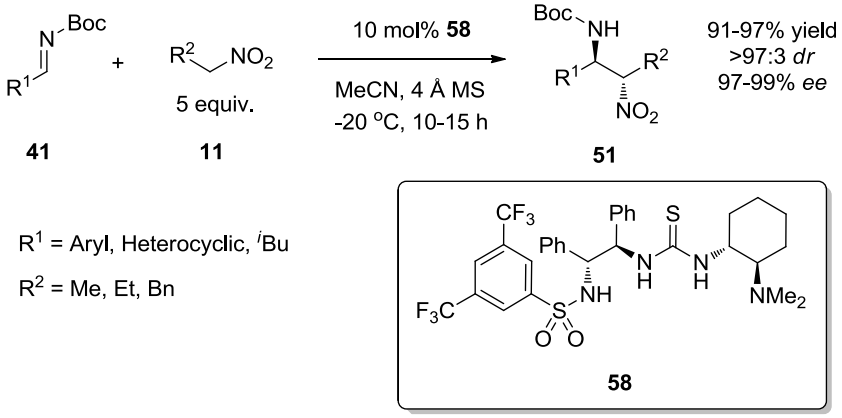


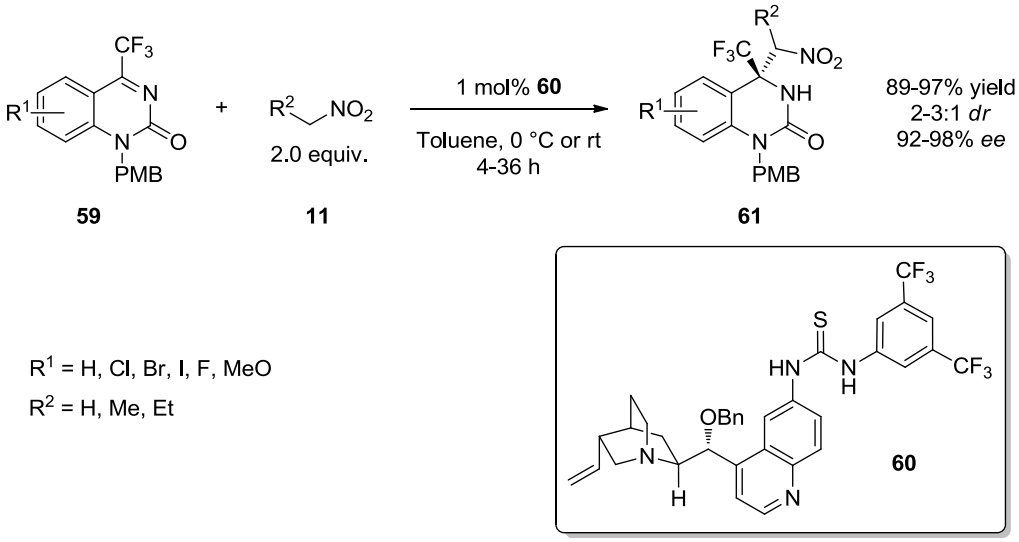
Figure 3. Palomo's transition states for phase-transfer catalysed nitro-Mannich reaction

In 2008, C. Wang *et al.* reported the most selective organocatalytic nitro-Mannich reaction to date.[36] Using thiourea **58** with two chiral diamine groups, exceptional diastereoselectivity and enantioselectivity was obtained for the reaction between *N*-Boc imines **41** and nitroalkanes **11** (Scheme 23). Unfortunately, despite the excellent stereoselectivity the reaction requires 5 equivalents of nitroalkane **11** to obtain good yields within the reported reaction time.



Scheme 23. Highly *anti* selective thiourea catalysed nitro-Mannich reaction

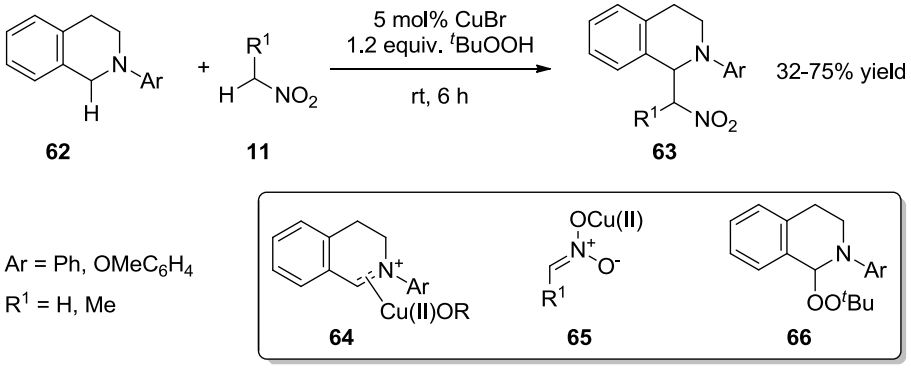
In 2011, W. Wang reported the first organocatalysed nitro-Mannich reaction of ketimines.[37] Using only 1 mol% of cinchona-alkaloid derived thiourea **60**, the authors were able to couple a variety of nitroalkanes to trifluoromethyl ketimines **59** in excellent yields and enantioselectivity albeit moderate diastereoselectivity (Scheme 24). Unfortunately, the scope of the reaction could not be extended beyond trifluoromethyl ketimines and when simple methyl ketimines were used no reaction was observed.



Scheme 24. Asymmetric nitro-Mannich reaction of trifluoromethyl ketimines

1.1.6 Miscellaneous nitro-Mannich reactions

So far this introduction has dealt exclusively with "classical" nitro-Mannich reactions. Recently however, there have been reports of less conventional reactions such as oxidative nitro-Mannich reactions and nitro-Mannich reactions of isoquinolines. This chapter will briefly examine some of these exciting new approaches to the *β*-nitroamine framework.



Scheme 25. Cross-dehydrogenative coupling reaction and tertiary amines and nitroalkanes

In 2005, Li *et al.* reported an oxidative nitro-Mannich reaction using a copper catalyst and *tert*-butylhydroperoxide (TBHP) as an oxidant.[38] This so-called cross-dehydrogenative coupling (CDC) reaction was able to couple nitromethane and nitroethane with a variety of amines bearing *α* sp^3 C-H bonds in varying yields (Scheme 25). The authors were unsure about the reaction mechanism but proposed that intermediates such as **64**, **65** and **66** are most likely to be involved.

Li's group have since reported some improvements to their procedure enabling the amount of nitroalkane to be lowered to two equivalents,[39] and the use of molecular oxygen instead of the explosive *tert*-butylhydroperoxide.[40] The group of Klussmann have performed detailed mechanistic work on both the TBHP and molecular oxygen reactions and have proposed the following mechanisms (Figure 4).[41]

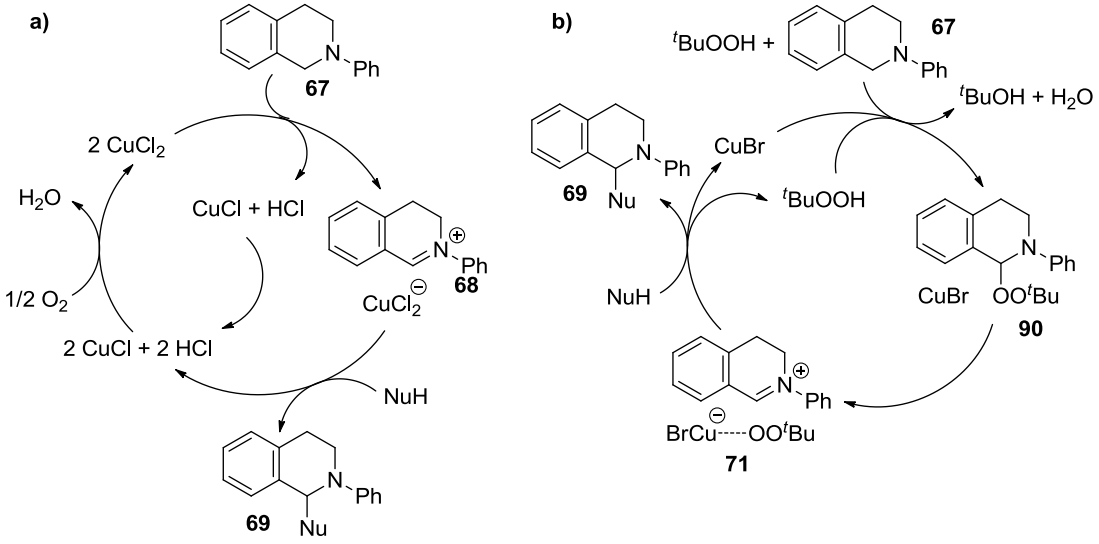
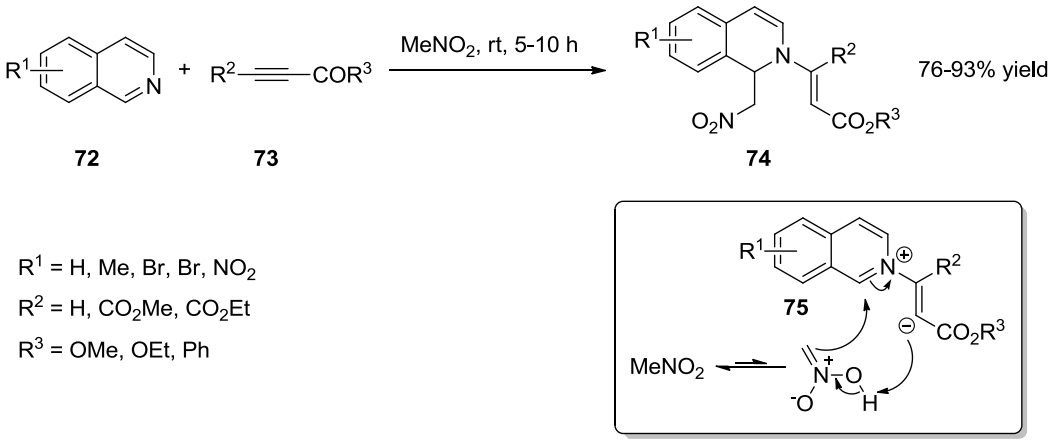


Figure 4. Mechanisms for CDC reaction when using A) O_2 and B) TBHP as oxidants

The groups of Todd,[42] Liang,[43] and Stephensen,[44] have also reported CDC reactions using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), hypervalent iodine species $PhI(OAc)_2$ and an Ir visible light photoredox catalyst respectively. However, as yet no group have been able to develop an enantioselective CDC reaction so the utility of this reaction is still somewhat limited.



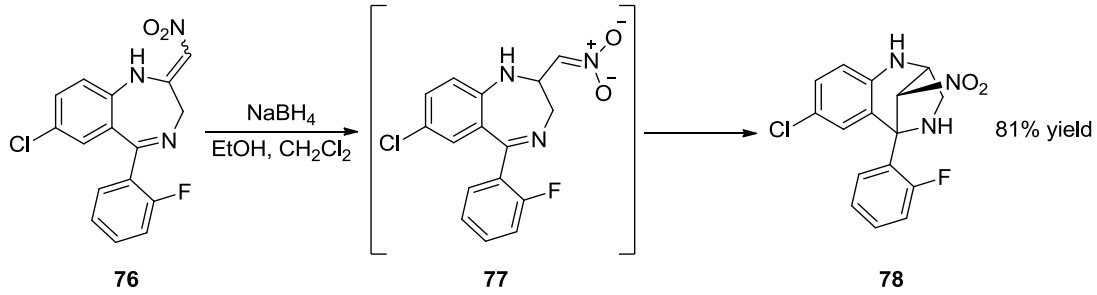
Scheme 26. Nitro-Mannich reaction of activated isoquinolines

Another non-classical reaction reported in the literature is the nitro-Mannich reaction of isoquinolines. Yadav *et al.* published a three-component synthesis of nitromethyl

derivates of 1,2-dihydroisoquinolines.[45] The authors were able to couple a variety of isoquinolines **72**, after activation with alkynes **73**, with nitromethane to give the desired 1,2-dihydroisoquinolines **74** in good yield. The authors proposed the reaction proceeded with initial activation of the isoquinoline to give Zwitter ion **75** which then underwent a nitro-Mannich reaction with the *aci* form of nitromethane.

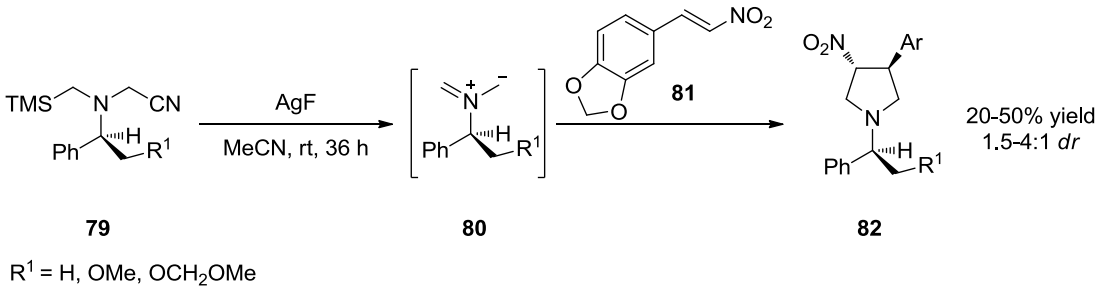
1.1.7 Conjugate addition/nitro-Mannich reactions

In addition to the standard deprotonation strategy to form the reactive nitronate species of the nitro-Mannich reaction, there have also been a number of reports where a conjugate addition to a nitroalkene has led to the formation of the nitronate species which has then undergone an *in situ* nitro-Mannich. The first example of such a reaction came in 1978 when Walser *et al.* unexpectedly observed a nitro-Mannich reaction whilst investigating pharmacologically active benzodiazepines.[46]



Scheme 27. Unexpected reductive nitro-Mannich reaction

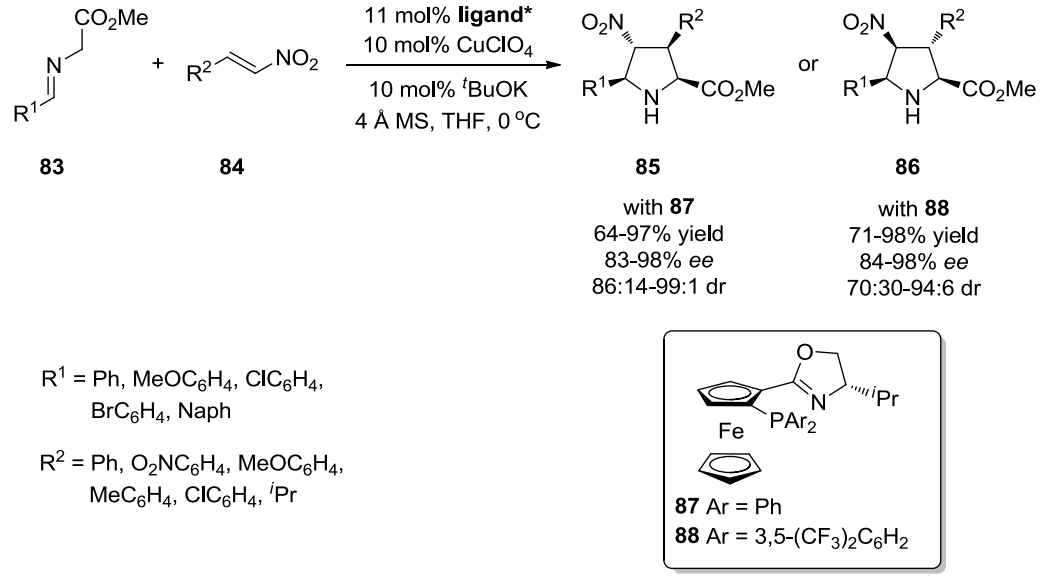
The authors were attempting to reduce nitroalkene **76** with sodium borohydride but instead observed an instantaneous nitro-Mannich reaction to give *β*-nitroamine **78** in an 81% yield (Scheme 27). The structure was also confirmed by single crystal X-ray analysis.



Scheme 28. First reported [3+2] cycloaddition nitro-Mannich reaction

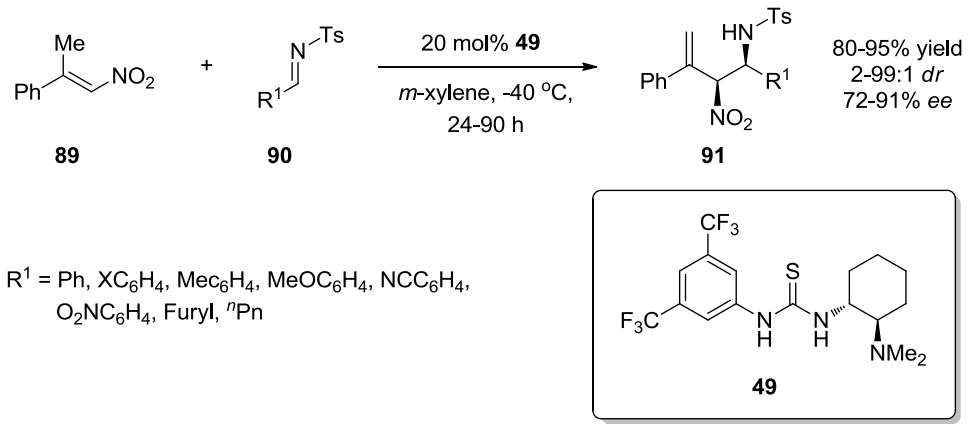
In 1985, the group of Padwa reported the [3+2] cycloadditions of chiral azomethine ylides **80** with a variety of dipolarophiles including nitroalkene **81**.[47] The authors

used AgF to form the azomethine ylides from α-cyanoaminosilanes **79**, giving desired 3-nitropyrrolidines **82** in low to moderate yields and diastereoselectivity (Scheme 28). Although, [3+2] cycloadditions often proceed in a concerted manner, the majority of [3+2] cycloadditions involving nitroalkenes have been shown to progress in a stepwise manner.[48] This is due to the high electrophilicity of the π-deficient nitroalkene, and as such these [3+2] cycloadditions with azomethine ylides can be thought of as nitro-Mannich reactions.



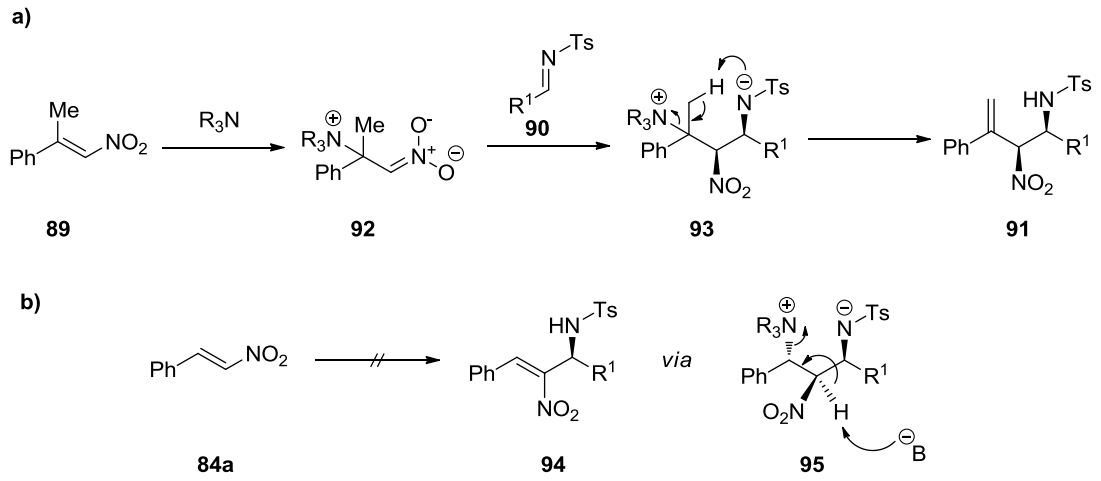
Scheme 29. Enantioselective catalytic [3+2] cycloaddition nitro-Mannich reaction

Since this publication there have been a number of asymmetric [3+2] cycloaddition nitro-Mannich reactions.[49] Hou has reported the broadest reaction scope using a chiral ferrocene ligand and copper catalyst.[49c] Amazingly, a simple change in the electronics of the aryl groups of the phosphine of the catalyst resulted in a switch in the *endo*/*exo* selectivity allowing the authors to synthesise both isomers (Scheme 29).



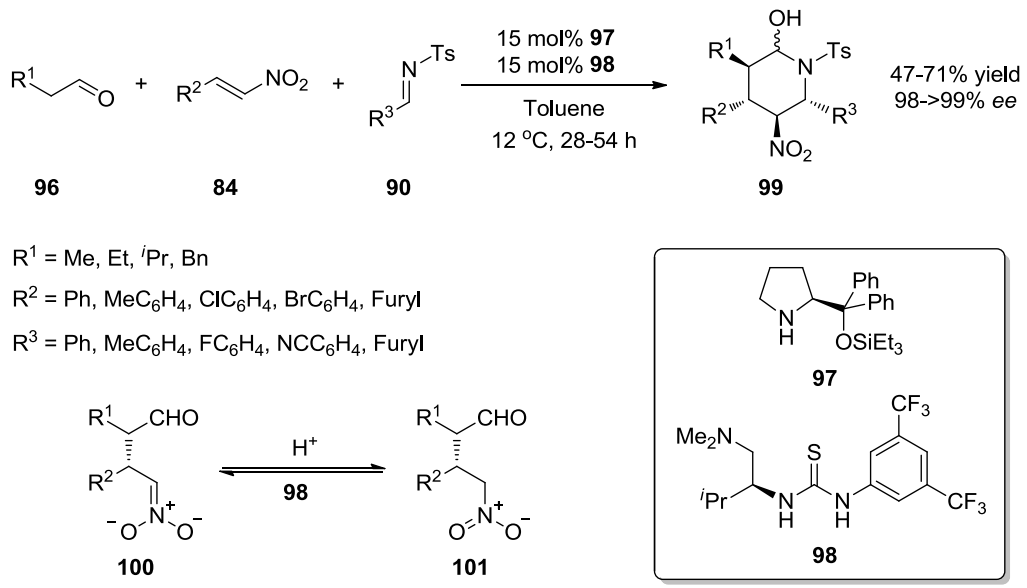
Scheme 30. Morita-Bayliss-Hilman type nitro-Mannich reaction

In 2009, a report by Xu *et al.* detailed the use of Takemoto's catalyst **54** in a Morita-Baylis-Hillman (MBH) type nitro-Mannich reaction.[50] The authors were able to react nitrostyrene **89** with a range of *N*-tosylated imines **90** to produce the desired *β*-nitroamines **91** possessing a *γ*-methylene (Scheme 30). Interestingly, when simple *β*-nitrostyrene **84a** was used instead of nitroalkene **89**, no reaction was observed. The authors believe this suggests that an intramolecular deprotonation is required to eliminate the catalyst from intermediate **93** and produce the product (Scheme 31).



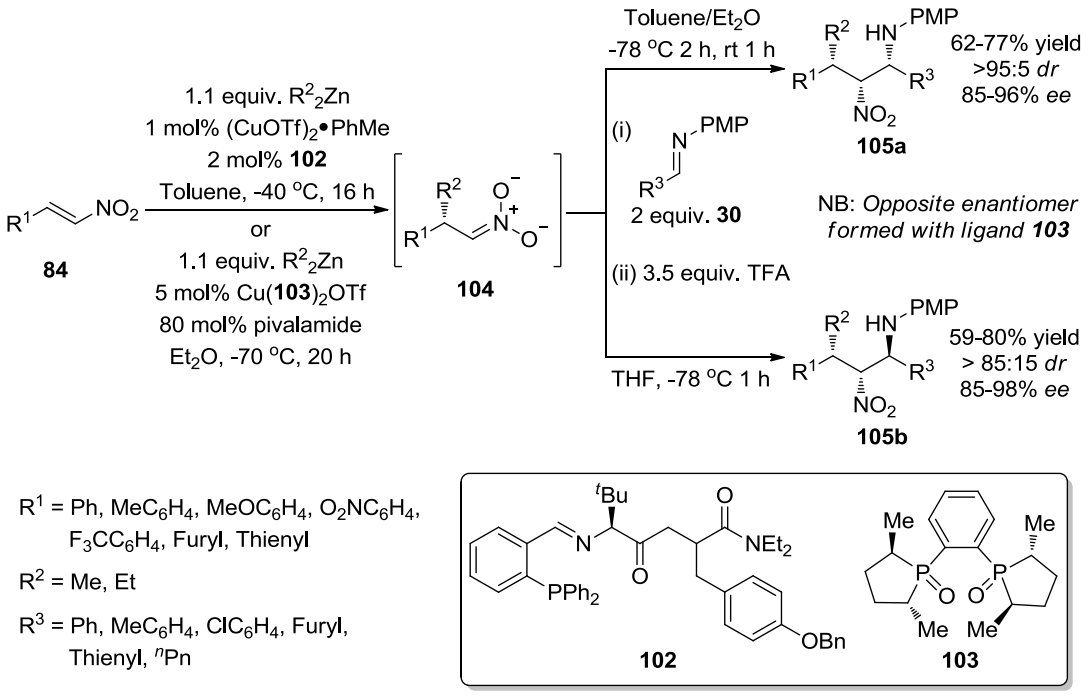
Scheme 31. Proposed mechanism of MBH type nitro-Mannich reaction

In 2010, the group of Xu reported the enantioselective synthesis of piperidines **99** using a nitro-Michael/nitro-Mannich/cyclisation sequence.[51] The authors utilised two organocatalysts (pyrrolidine **97** and thiourea **98**) in an one-pot reaction to promote the desired reaction in moderate to good yields, excellent enantioselectivity and as single diastereomers (Scheme 32). The authors did not discuss the mechanism of the reaction nor did they disclose which if any of the intermediates are isolated after chromatography. Therefore we can only speculate as to whether nitronate **100** formed by the nitro-Michael reacts immediately or if it exists in an equilibrium with nitroalkane **101**. There have been a number of reports of similar reactions since using just one organocatalyst,[52] however these reactions proceed in a stepwise manner requiring addition of an external base after the nitro-Michael reaction. As such the nitro-Mannich reaction is activated by the standard means of deprotonation and shall not be further discussed in this section.



Scheme 32. An one-pot nitro-Michael/nitro-Mannich/cyclisation to piperidines

More recently the Anderson group have examined the addition of organometallic reagents to nitroalkenes and their subsequent nitro-Mannich reactions.[53] Using Hoveyda's (**102**) and Charette's (**103**) catalysts for dialkyl zinc additions to nitroalkenes,[54] the authors were able to form nitro-Mannich products with excellent diastereo- and enantioselectivity when reacted with *N*-PMP imines **30** in the presence of trifluoroacetic acid (Scheme 33).



Scheme 33. One-pot dialkyl zinc addition/nitro-Mannich reaction of nitroalkenes

The authors observed a remarkable dependency of diastereoselectivity on solvent selection. Weak Lewis base solvents such as diethyl ether and toluene gave *syn,syn* nitro-Mannich products **105a** whereas more coordinating solvents such as tetrahydrofuran favoured *syn,anti* diastereomer **105b**. This was proposed to be caused by the different solubilities of $Zn(O_2CCF_3)_2$ formed in the reaction. In toluene and diethyl ether, the zinc (II) trifluoroacetate precipitated out of solution whereas in tetrahydrofuran the salt remained in the solution. The authors suggest that the reaction may proceed by two mechanisms, one where the zinc salt is involved in a closed transition state and another where no zinc is present and hence a mechanism *via* an open transition state operates. In toluene or diethyl ether there is no zinc to participate so the reaction proceeds *via* transition state **TS-6,** whilst in tetrahydrofuran the zinc acts as a chelating metal in transition state **TS-7** (Figure 5).

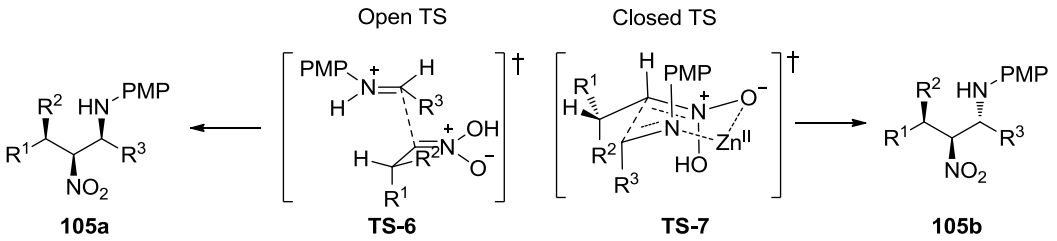


Figure 5. Proposed transition states leading to *syn* and *anti* nitro-Mannich products

The Anderson group have also expanded this methodology by using ethyl (*E*)-3-nitroacrylate as the nitroalkene to form nitro-Mannich products which cyclise to give pyrrolidinones.[55]

1.2 Synthetic utility of nitro-Mannich products

1.2.1 Overview

The products of the nitro-Mannich reaction, *β*-nitroamines, contain two nitrogens in differing oxidation states allowing for complete chemoselectivity in subsequent transformations. This synthetic versatility gives *β*-nitroamines great potential for their application in synthesis. This chapter will briefly discuss some of the possible transformations of *β*-nitroamines and showcase their potential application as key intermediates in the total synthesis of some complex natural products and pharmaceuticals, some examples of which are shown in figure 6.

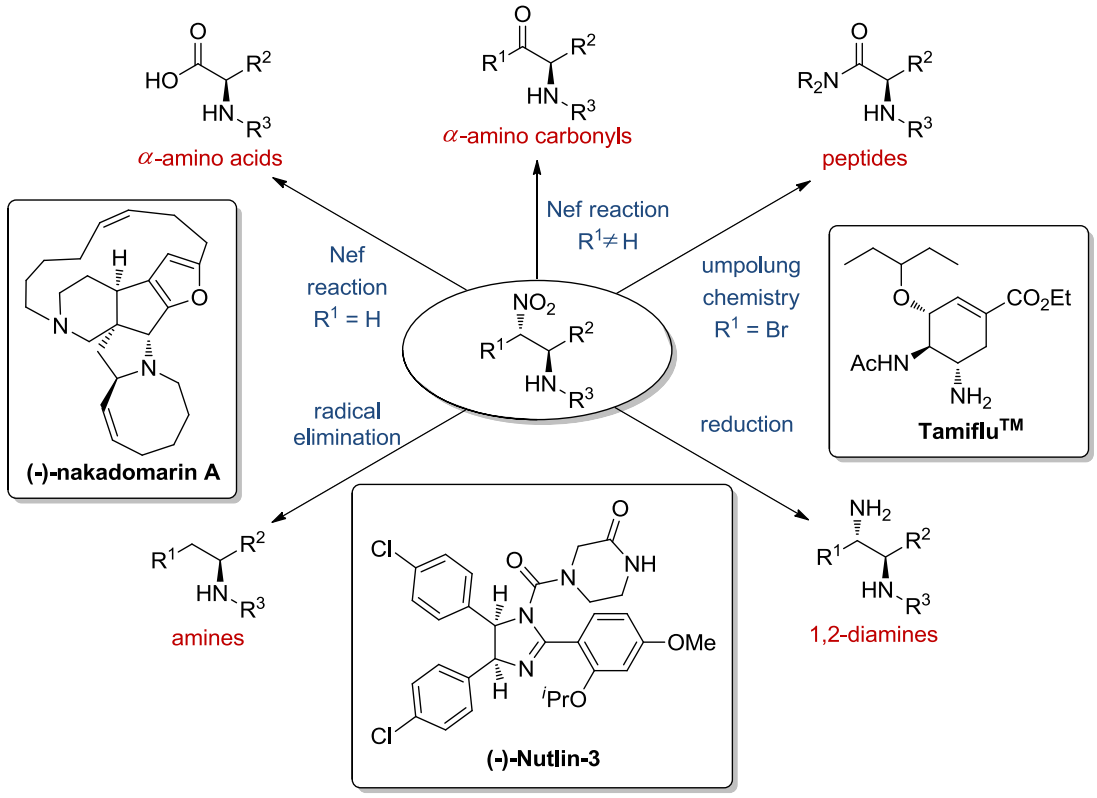
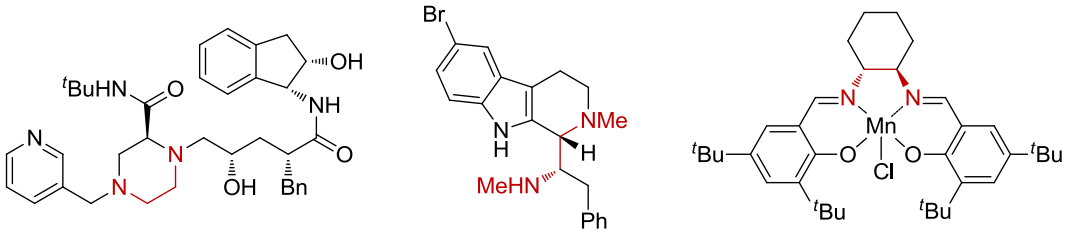


Figure 6. Examples of the synthetic utility of *β*-nitroamines

1.2.2 Nitro reduction

Probably the most useful transformation of the nitro-Mannich products is the reduction of the nitro group to give vicinal diamines. In addition to the fact that the reaction is more atom economical than the other transformations shown in figure 6,

there are also a limited number of ways of synthesising 1,2-diamines efficiently.[56] Vicinal diamines are important structural motifs and have many applications in a variety of natural products, pharmaceuticals and catalysis (Figure 7). As such, efficient syntheses to produce 1,2-diamines are highly desirable.



Indinavir™ *anti-HIV*

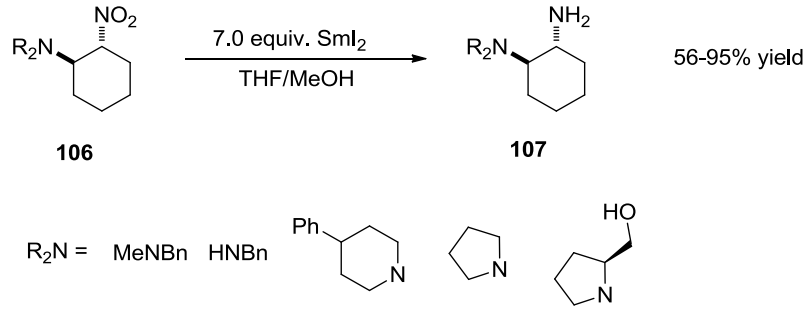
Eudistomidin B *cytotoxic*

Mn-Salen Complex *chiral epoxidation catalyst*

Figure 7. Examples of importance of vicinal diamines

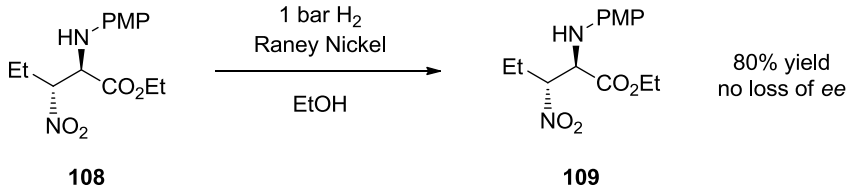
The reduction of aromatic nitro groups has been well documented in the literature and these reactions have been performed on industrial scale as they provide the most important method for the synthesis of anilines. The reduction of aliphatic nitro groups however, possesses different challenges.[57] The reactions are frequently more sluggish than their aromatic counterparts and are often complicated by unwanted side-products. Despite these challenges, there are a variety of methods known to reduce aliphatic nitro compounds, including *β*-nitroamines which also often have a tendency to undergo retro-addition. This section will now discuss some of the previously used methods to achieve this.

The first nitro reduction of *β*-nitroamines was performed by Duden *et al.* using stannous chloride in hydrochloric acid.[10a] The reduction was performed as the product from the nitro-Mannich was too unstable. However, the yield of the reaction (26%) was poor. Other early conditions used to reduce *β*-nitroamines include the use of aluminium amalgam,[10b] and high pressure hydrogenation with Raney nickel.[8] In recent years much milder and better yielding reactions have been developed. In 1993, Sturgess's group reported the rapid and mild reduction of *β*-nitroamines **106**, formed *via* Michael addition of amines to nitroalkenes, using the single electron transfer reducing agent samarium (II) iodide (Scheme 34).[58] This was the first report of a reduction of unstable *β*-nitroamines that could tolerate a range of substrates, giving the desired diamines in good yields. This SmI_2 reduction was then later utilised by the Anderson,[5] and Shibasaki groups to form vicinal diamines.[15,16]



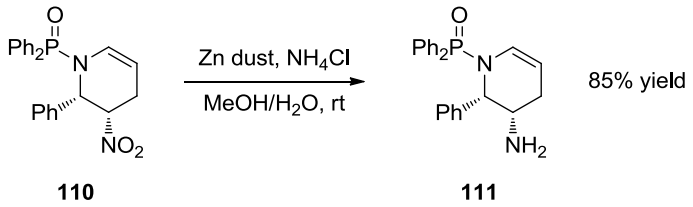
Scheme 34. Samarium (II) iodide reduction of *β*-nitroamines

Jørgensen *et al.* reduced nitro-Mannich product **108** *via* catalytic hydrogenation with Raney nickel at atmospheric pressure over two days in good yield. These conditions are distinctly milder than those previously reported (34 bar) by Senkus and Johnson for the reduction of nitro-Mannich products in 1946.[8]



Scheme 35. Raney nickel reduction of nitro-Mannich product

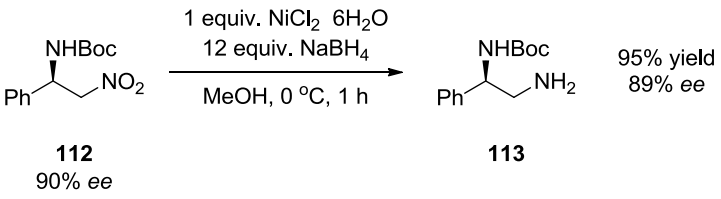
Another commonly used protocol for the reduction of nitro-Mannich products uses zinc powder in an acidic media. This method was first used for *β*-nitroamines in Shibasaki's synthesis of CP-99994, giving the desired diamine in 85% yield (Scheme 36).[59] There have since been a variety of other nitro reductions using Zn including many in hydrochloric acid solutions such as those reported by Feng,[26] and Anderson.[53]



Scheme 36. Nitro reduction using zinc dust in acid

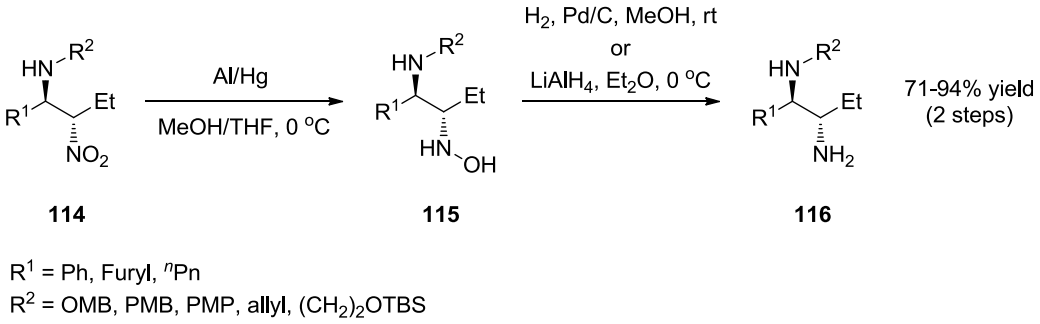
Another popular reagent for the reduction of *β*-nitroamines is nickel boride. This is typically formed *in situ* from $NiCl_2 \bullet 6H_2O$ and $NaBH_4$. Bernardi and Ricci first demonstrated its use in the reduction of *β*-nitroamines during their synthesis of HIV protease inhibitors. It has since been applied by the groups of Shibasaki,[24] and

Takemoto (Scheme 37)[30] to effect nitro reductions in excellent yields. Johnston *et al.* have also used $CoCl_2$ in place of $NiCl_2$ in similar reductions.[60]



Scheme 37. Nickel boride reduction of nitro-Mannich product

An alternative reduction protocol that has been frequently used is aluminium amalgam reductions. This method has been shown to be particular successful for sensitive substrates by the Anderson group.[61]



Scheme 38. Aluminium amalgam reduction of β-nitroamines

It was found that the aluminium amalgam gently reduced the nitro-Mannich products **114** to stable hydroxylamines **115**. Further reduction using $LiAlH_4$ or Pd/C hydrogenation could then give desired diamines **116** in excellent yields (Scheme 38).

1.2.3 Nef reaction

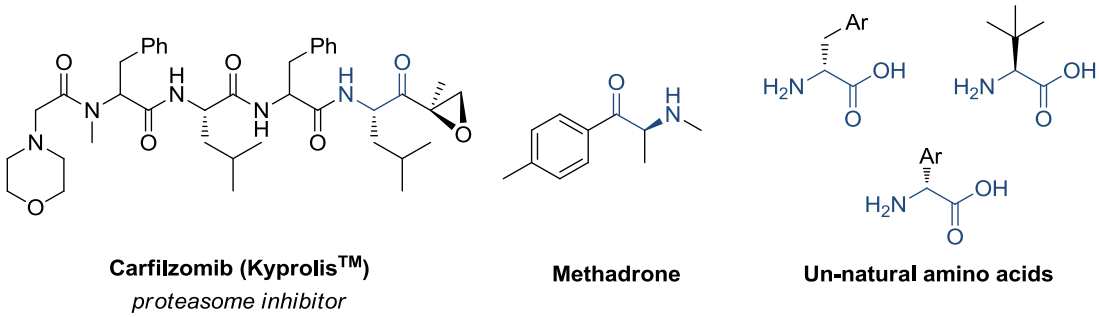
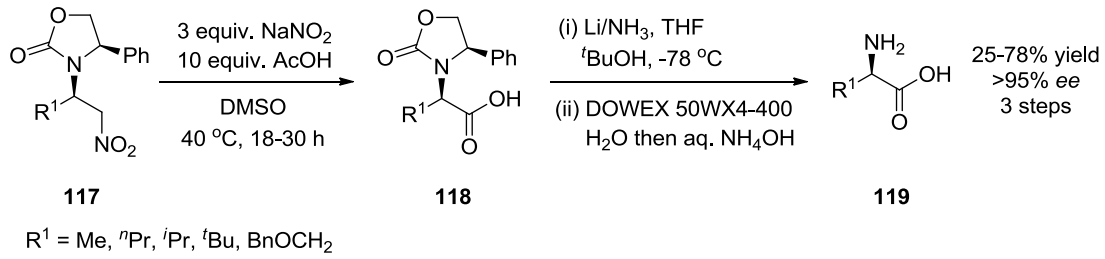


Figure 8. Examples of important α-amino carbonyl containing compounds

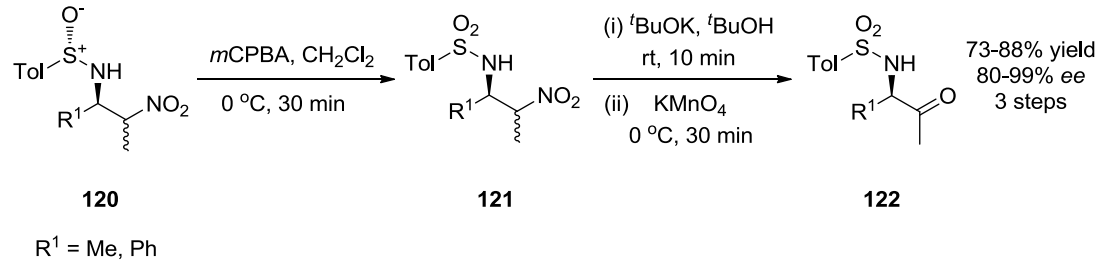
The Nef reaction is the direct conversion of a nitro group to a carbonyl group.[62] In particular, a nitro-Mannich/Nef reaction route has the potential to provide an efficient route to highly enantioselective un-natural α-amino acids. In addition, the Nef

reaction of *β*-nitroamines could furnish *α*-amino ketones, which are found in several important medicines and biologically active natural products (Figure 8). The first examples of Nef reactions on *β*-nitroamines **117** were reported in 1998 by Mioskowski *et al.* using sodium nitrite and acetic acid in DMSO.[63] Subsequent removal of the chiral auxiliary gave desired *α*-amino acids **119** in variable yields. Since this publication many other groups have also applied this methodology and showed a neglible loss of enantioselectivity during the transformation.[11,22,30,64] There have also been reports of Nef reactions to give *α*-amino acids using potassium permanganate,[65] and ozone.[66]



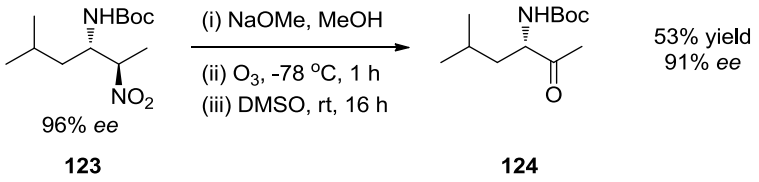
Scheme 39. Nef reaction of *β*-nitroamines to give *α*-amino acids

There have been few reported Nef reactions of nitro-Mannich products to give *α*-amino ketones. The first was reported by Ruano and Cid *et al.* using potassium permanganate.[13a] The authors initially attempted the Nef reaction using sulfinyl-*β*-nitroamines **120** but all conditions tested failed to give the desired products. However, when converted to sulfonyl-*β*-nitroamines **121** the desired Nef reaction could be performed in high yields (Scheme 40).



Scheme 40. Nef reaction using $KMnO_4$ to give *α*-amino ketones

Ellman's group have also reported a Nef reaction to give an *α*-amino ketone but instead using ozone.[67] This reaction was performed to confirm the absolute stereochemistry of the nitro-Mannich product and only proceeded with a moderate yield (51%) (Scheme 41).

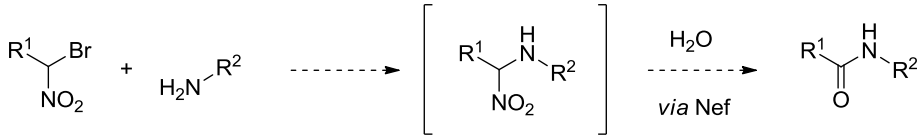


123 **124**

Scheme 41. Nef reaction using ozone

1.2.4 Peptide synthesis *via* umpolung reactivity

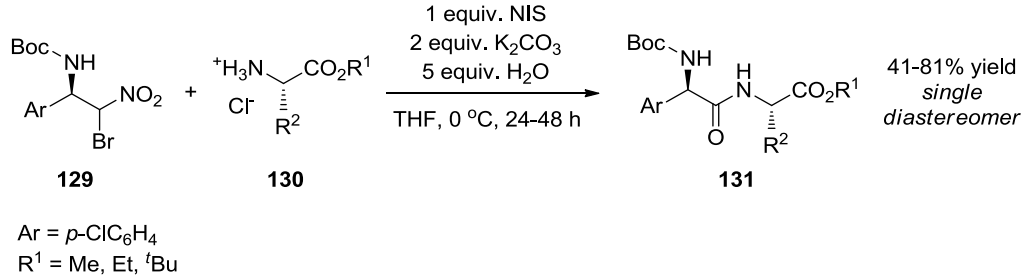
In 2010, the group of Johnston reported an innovative new method for the synthesis of amide and peptide bonds.[68] The authors hypothesised that *α*-bromo nitroalkane **125** could provide the correct oxidation state for a coupling with an amine to give *α*-amino nitroalkane **127**. Subsequent hydrolysis with water *via* a Nef-like reaction could then form amide **128** (Scheme 42). When attempting such a reaction, after 10 days a trace amount of desired product and also some de-brominated nitroalkane were observed.



125 **126** **127** **128**

Scheme 42. Initial proposed reaction

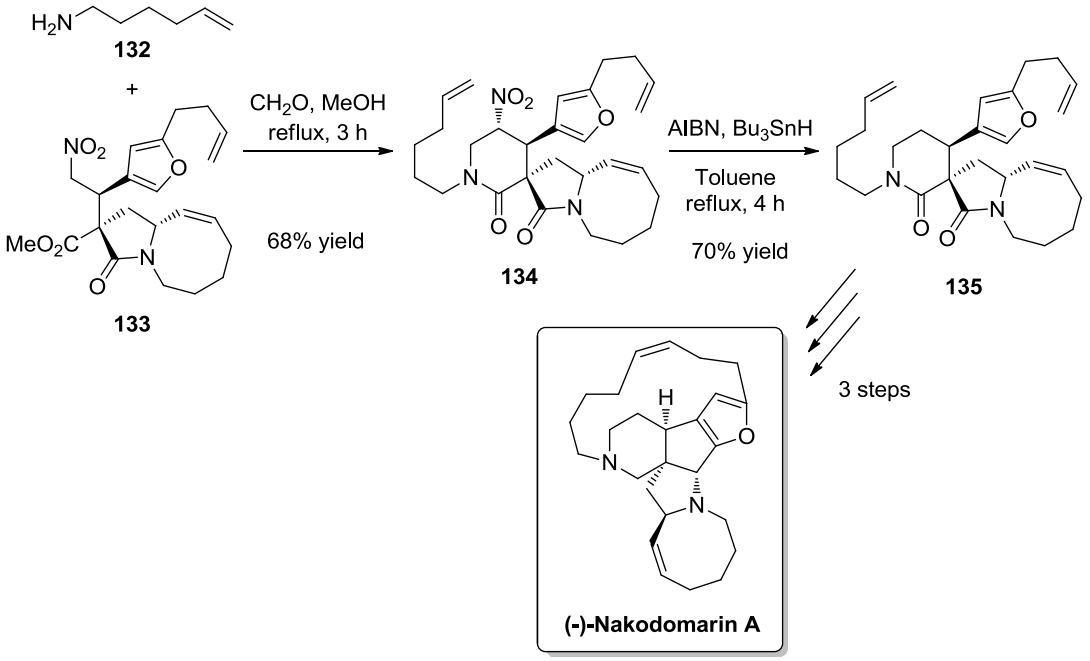
From this observation it was thought that the reaction may be proceeding through an umpolung reaction with an *N*-bromo amine and nitronate pair, formed *via* bromonium transfer. The authors consequently examined the action of an electrophilic halogen source, *N*-iodosuccinimide (NIS), in the reaction and observed substantial amounts of desired product. After optimisation of the reaction conditions the authors were able to form a variety of different amides using this methodology. They subsequently turned their attention to nitro-Mannich products **129** in order to synthesise a range of different peptides **131** in moderate to good yields and crucially without any loss of stereoselectivity (Scheme 43).



Scheme 43. Aryl glycine couplings to a range of amino acids

1.2.5 Radical and ionic denitration

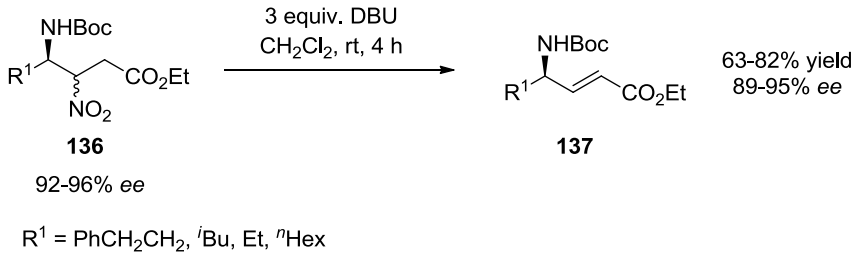
Although not the most atom efficient use of a nitro-Mannich reaction, the radical elimination of the nitro group from nitro-Mannich products has been utilised numerous times in the total synthesis of a variety of important products. Despite this poor atom economy this transformation still has a place in modern organic chemistry due to the need for highly stereoselective syntheses of amines.



Scheme 44. Dixon's total synthesis of (-)-Nakodomarin a featuring a radical denitration

Radical denitration with Bu_3SnH and AIBN has been the most commonly applied form of elimination of the nitro group from *β*-nitroamines. There have been a series of total syntheses that have utilised this strategy,[69] some of which used the nitro-Mannich reaction to form the starting materials.[70] The most recent example of such a transformation is in Dixon's total synthesis of Nakodomarin A.[70c-f] The authors first formed 6-membered lactam **134** *via* a nitro-Mannich/lactamisation cascade

reaction. Afterwards the nitro group was removed under standard conditions using Bu_3SnH and AIBN to form intermediate **135**. With this in hand the authors could complete the synthesis of (-)-Nakodomarin A in three more steps.



Scheme 45. Ionic denitration of nitro-Mannich products

Ionic denitration requires an acidic *β*-hydrogen in order to eliminate the NO_2 group and results in the formation of a double bond. Palomo *et al.* have successfully performed this reaction on a variety of nitro-Mannich products **136** using DBU as base. This process represented a new entry to the synthesis of enantiopure vinylogous amino acids.

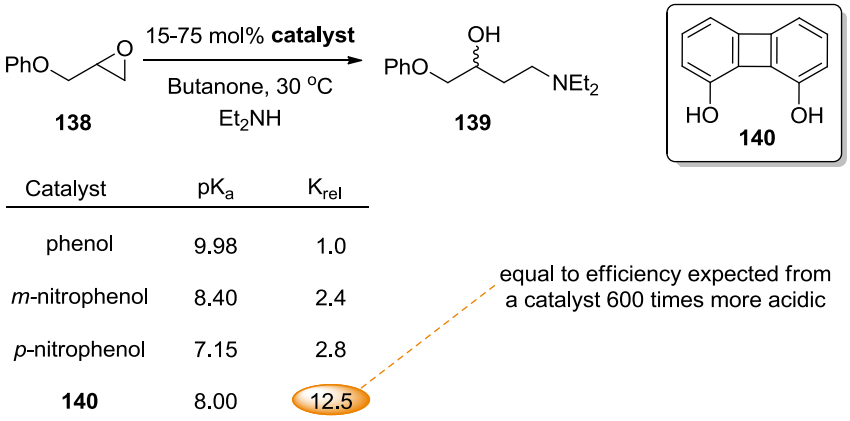
1.3 Thiourea organocatalysis

1.3.1 Overview

Lewis acids have long been regarded as a crucial element of the synthetic chemists' toolbox and have a longstanding use as catalysts to activate electrophiles. Far-reaching research in ligand design and Lewis acid catalysis has resulted in a huge array of chiral catalysts that can selectivity control many reactions.[71] However, such catalytic systems have their limitations: Firstly, several metals are known to be toxic, and as such their use in industries such as the pharmaceutical industry would ideally be avoided. Secondly, many commonly used Lewis acid metals possess strong oxophilicity or are moisture sensitive limiting their practical use. Thirdly, many metals used in catalysis, particularly rare earth metals, are very expensive limiting their use in large scale processes. Finally, there is a limited supply of many metals and their use is not sustainable long term. Organocatalysis has emerged as an alternative method over the past decade with the potential to supersede traditional metal catalysis in many areas. Thioureas have been shown to be excellent catalysts to activate electrophilic components, particular in reactions that can undergo general acid catalysis. In this sense they offer a complimentary approach to Lewis acid catalysis and the recent field of chiral Brønsted acid catalysis.[72] Thioureas offer many potential advantages over Lewis acid catalysts in that they are potentially significantly cheaper than many commonly used metals, they may be less toxic than many heavy metal catalysts and their use may be more sustainable in the long term. However, there are also limitations and currently most thiourea catalysed reactions require large catalyst loadings (typically 5-10 mol%). Presumably this is due to a weak activation of the electrophiles compared to Lewis acids. There have been several reviews of thiourea organocatalysis in recent years.[73] Due to the large size of the research in this field, it would be impossible to cover every development in this introduction. Therefore, this section will attempt to introduce thiourea organocatalysts through the early research which has led to their widespread use and highlight some of the key possible transformations in particular those involving additions to imines and nitroalkenes.

1.3.2 Background and early research

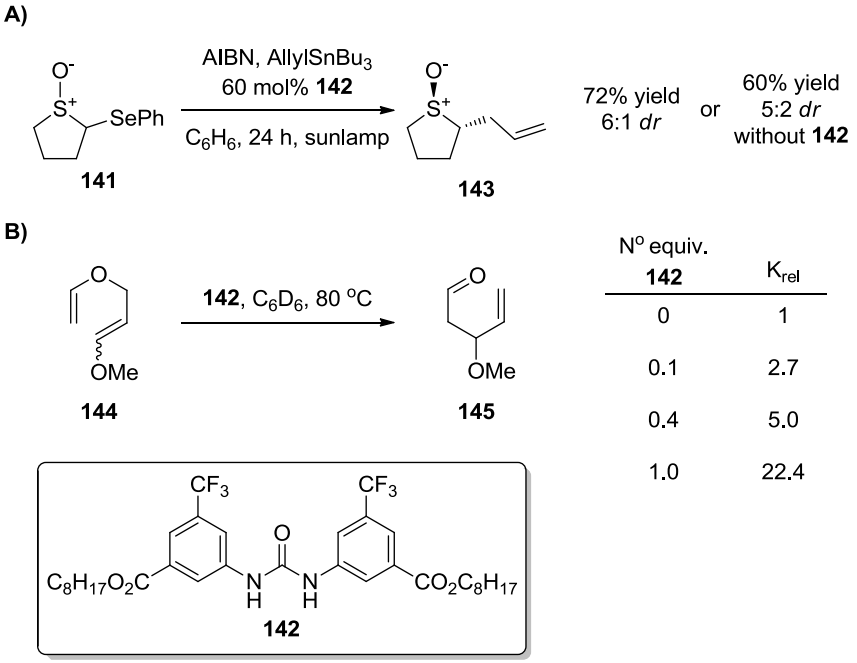
Although thioureas have been one of a number of organocatalysts at the forefront of asymmetric catalysis for around a decade the basis for their use was first reported much earlier. In 1984, Hine *et al.* showed a variety of phenols could catalyse the addition of secondary amines to glycidyl phenyl ether. They were able to show that a rigid biphenylenediol catalyst was able to promote the reaction significantly faster than standard phenols (Scheme 46).[74] If the reaction was solely promoted by acidity then to achieve such a rate of reaction, diol **151** would be expected to be 600 times more acidic than its actual pK_a. The authors proposed that the enhanced catalytic activity was the result of simultaneous donation of the two H-bonds. Later, a 1:1 solid-state structure of the catalyst and substrate gave support to this model.[75] Then in 1990, Kelly and co-workers reported a similar catalyst capable of promoting Diels-Alder reactions.[76]



Scheme 46. Biphenylenediol catalysed ring-opening of epoxide

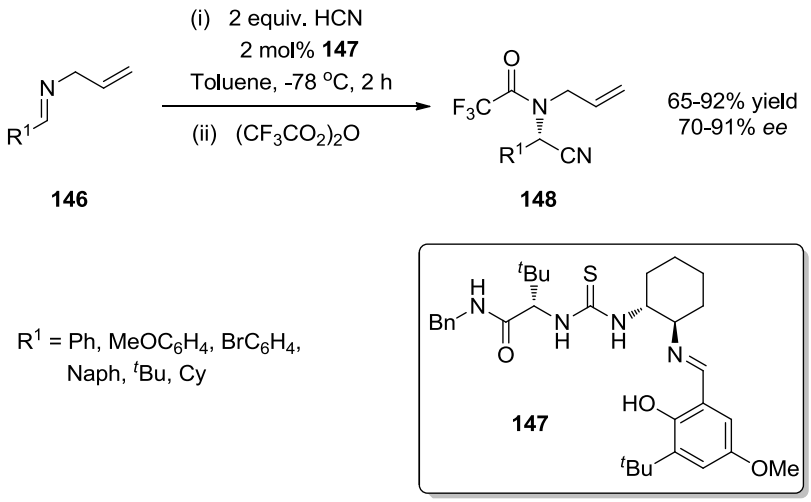
The next advance came towards the end of the same decade when Etter *et al.* reported co-crystallised structures of *N*-*N*'-diarylureas with a variety of Lewis basic functional groups such as nitros, ethers, ketones and sulfoxides.[77] Each implicated the donation of two H-bonds from the urea molecule to the Lewis base.

In 1994, Curran and co-workers reported a urea catalysed allylation of cyclic α-sulfinyl radicals with allyltributylstannane (Scheme 47, A).[78] In the following year the same authors reported a Claisen rearrangement of allyl vinyl ethers **144** also catalysed by urea **142** (Scheme 47, B).[79]



Scheme 47. Curran's urea catalysed allylation and Claisen rearrangements

Despite these early reports of H-bonding catalysts, researchers in the field of asymmetric catalysis failed to see the potential of such molecules as asymmetric catalysts. It wasn't until a serendipitous discovery from the Jacobsen group was reported that the field began to flourish. Jacobsen *et al.* were screening a variety of ligand and metal combinations for asymmetric Strecker reactions when it was observed that the reaction using thiourea **147** as a ligand proceeded with greater enantioselectivity in the absence of a metal.[80]

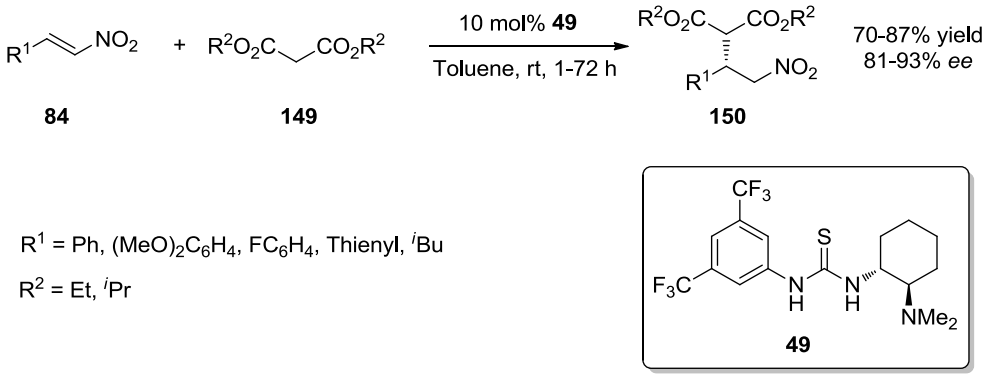


Scheme 48. First asymmetric reaction catalysed by a thiourea

At low temperatures the authors were able to add cyanide into a variety of allyl protected imines **146** in good to excellent yields and enantioselectivity (Scheme 48).

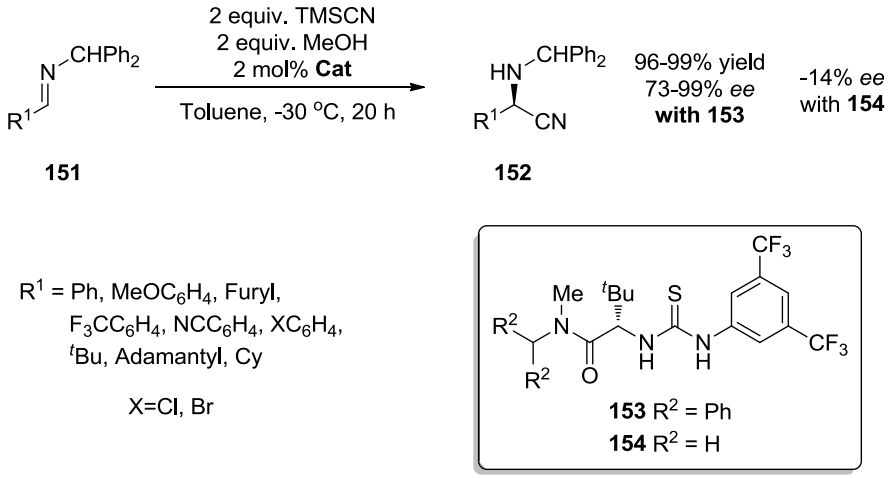
This report showed three important factors which would lead to significant interest in the field of organocatalysis. Firstly, that diaryl(thio)ureas are not essential for high catalytic activity; that the ability of (thio)ureas to catalyse organic transformations *via* H-bond is a general phenomenon; and that (thio)ureas containing chiral substituents are capable of transferring their chirality to the products of a reaction.

The final milestone, which really accelerated the field, was Takemoto's discovery of the relatively simple bifunctional thiourea catalyst **49** for the nitro-Michael reaction (Scheme 49).[81] The authors were able to add dialkyl malonates **149** to a variety of nitroalkenes **84** in good yields and with high to excellent levels of enantiocontrol.



Scheme 49. Asymmetric nitro-Michael addition of malonates to nitroalkenes

1.3.3 Thiourea catalysed additions to imine electrophiles



Scheme 50. Improved conditions for asymmetric Strecker reaction with simpler catalyst

Jacobsen's Strecker reaction was the first example of an enantioselective thiourea catalysed reaction of imines,[80] and consequently it was also that group that published the majority of the early research in the field. Further to their original paper, the

authors reported an extended scope of the reaction in 2000,[82] and a reaction of ketimines to form quaternary centres.[83] More recently, a much simpler catalyst structure and detailed mechanistic investigation has been reported by the same group (Scheme 50).[84] In order to minimise any exposure to toxic hydrogen cyanide, the authors used a combination of TMSCN and methanol to form HCN *in-situ*. Interestingly, large differences were observed in the stereoselectivity of the reaction with different amide substituents on the catalyst. It was noted that dimethyl amide **154** gave only 14% *ee*, whereas amido thiourea derivative **153** gave the desired product in 98% *ee*. Intrigued by this large difference and an interest in the mechanism the authors undertook an experimental and theoretical investigation into the origin of the enantioselectivity of the reaction.[84a] The computational studies were able to calculate several possible transition states for the reaction and the lowest energies for the transition states depicted in figure 9, explaining the observed levels of enantioselectivity.

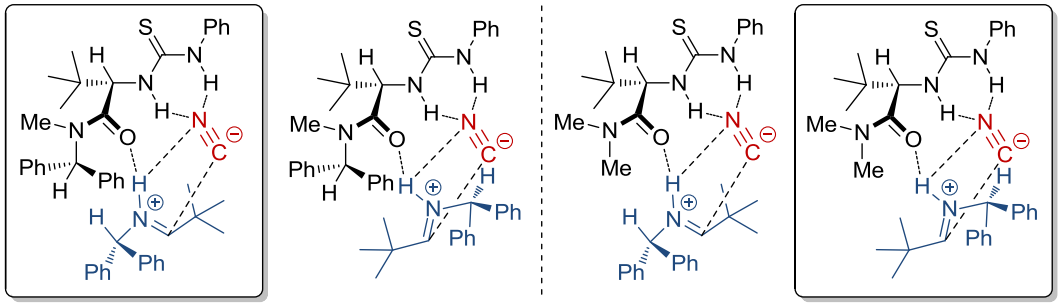
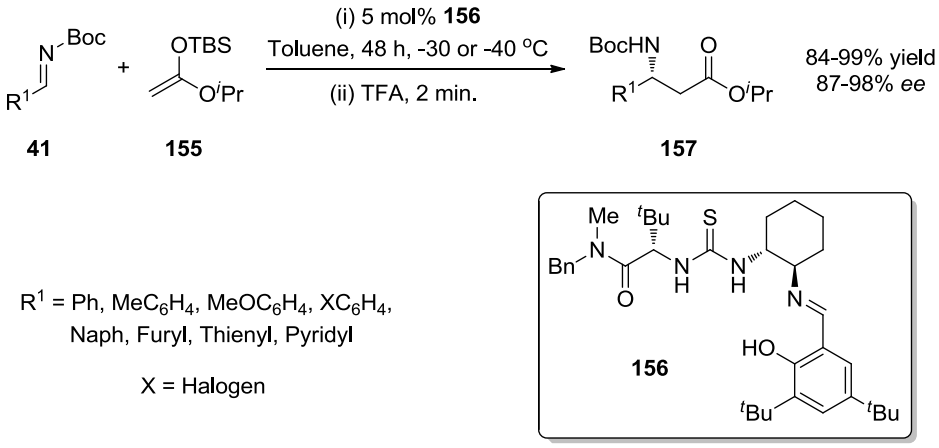


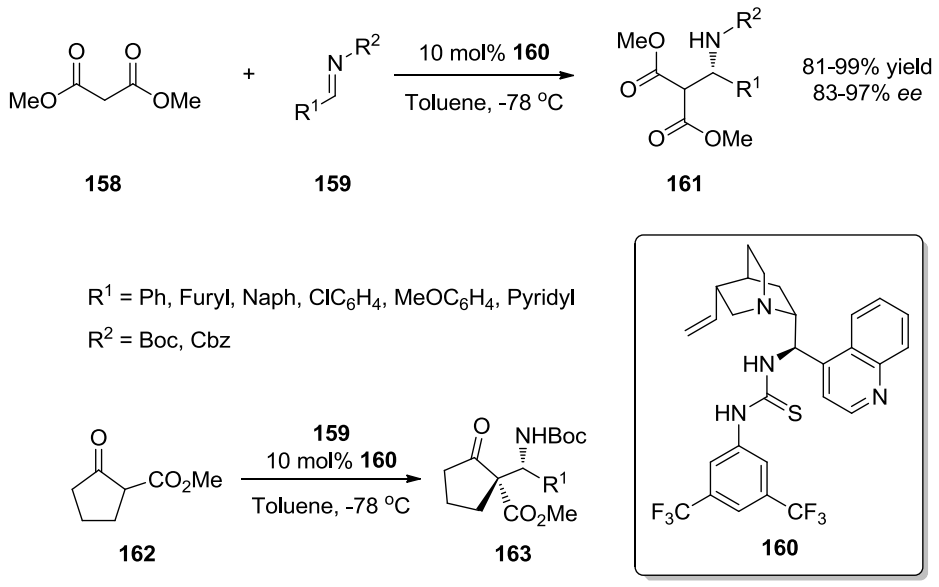
Figure 9. Calculated transition states for the thiourea catalysed Strecker reaction

In addition to the Strecker reaction the Jacobsen group have reported a number of other thiourea catalysed additions to imines. In 2002, the first thiourea controlled Mannich reaction was reported using silyl ketal acetal **155** and *N*-Boc protected imines **41 (**Scheme 51**)**.[85] Using thiourea **156** the authors were able to form a variety of *β*-amino esters **157** in excellent yield and enantioselectivity. The Jacobsen group have also applied a similar catalyst structure in the synthesis of chiral *α*-amino phosphonic acids.[86]



Scheme 51. Thiourea catalysed Mannich reaction of *N*-Boc imines

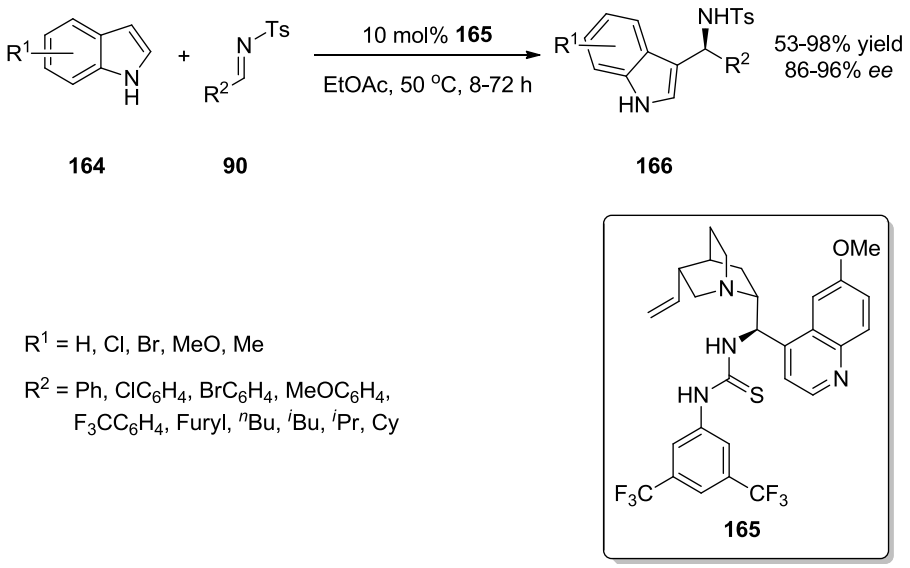
In 2006, Dixon *et al.* disclosed a chiral addition of malonates **158** into *N*-Boc and *N*-CBz imines **159** catalysed by thiourea **160** containing a Cinchona alkaloid skeleton.[87] High yields and enantioselectivities were obtained for the reaction, and formation of quaternary centres with high levels of selectivity was also possible when using methyl cyclopentanone-2-carboxylate **162** (Scheme 52). The authors were also able to de-carboxylate these Mannich products without observing racemisation. The groups of Deng, and Takemoto also reported similar reactions shortly after this publication.[88]



Scheme 52. Enantioselective Mannich reactions of malonates and *β*-keto esters

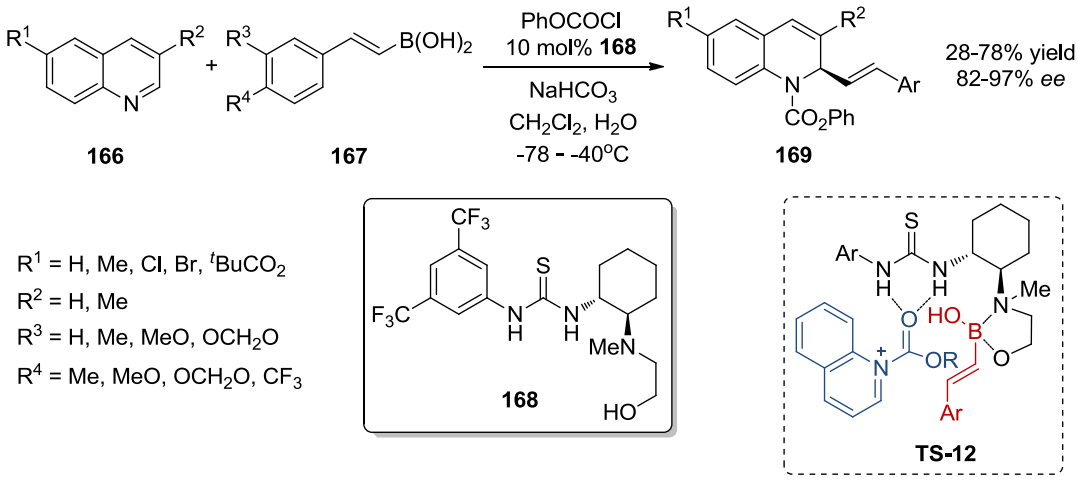
In the same year, Deng's group reported a thiourea catalysed asymmetric Friedel-Crafts reaction with imines.[89] Using cinchona-alkaloid thiourea **165** the

authors were able to add indoles **164** to *N*-tosyl protected imines **90** to give desired products **166** (Scheme 53).



Scheme 53. Thiourea catalysed Friedel-Crafts reaction of indoles with imines

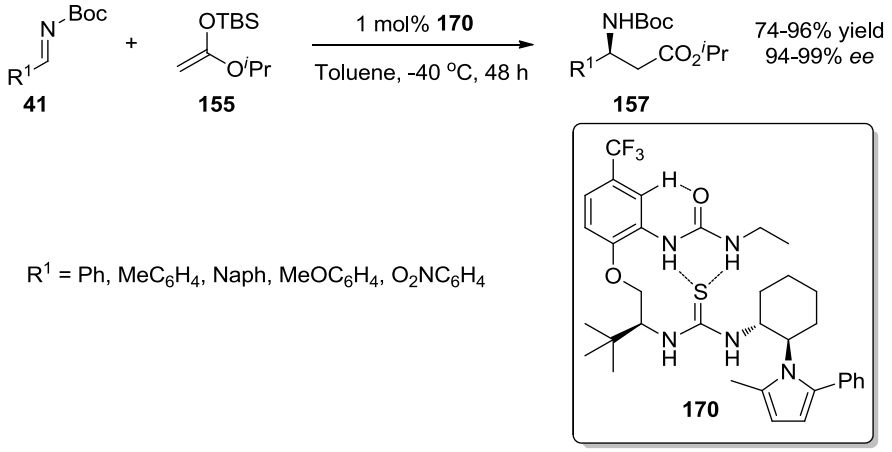
In 2007, Takemoto's group reported a Petasis-type reaction using 1,2-amino alcohol containing thiourea **168**.[90] The authors had hoped that by activating quinolines **166** *via* acylation with phenylchloroformate they would be able to promote the desired reaction as shown in **TS-12**. Using this activation strategy the authors were able to form desired products **169** using a variety of vinylboronic acids **167** in dichloromethane (Scheme 54). Interestingly, water and sodium bicarbonate were crucial additives required in order to obtain high enantioselectivities and good yields.



Scheme 54. Thiourea catalysed Petasis-type reaction of vinylboronic acids

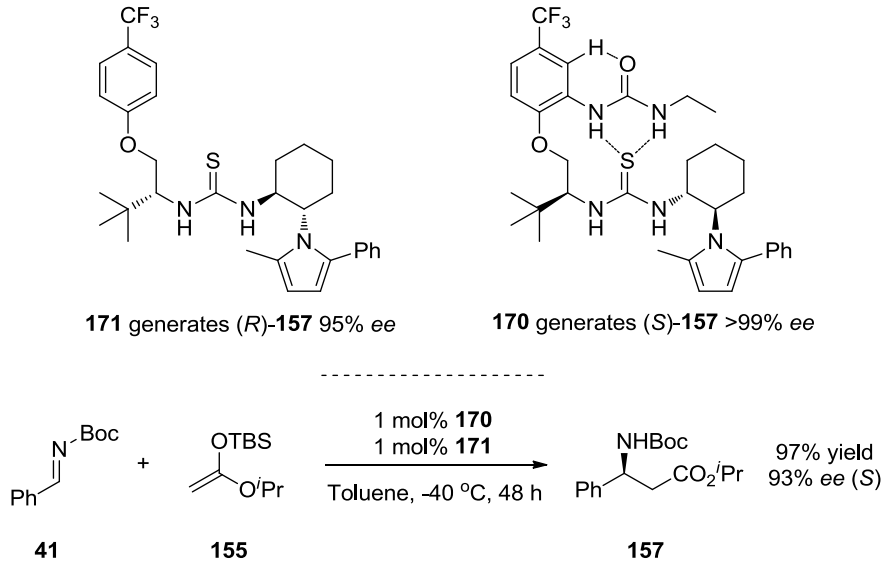
Another Mannich reaction was reported in 2009 by Smith's group using a new rationally designed thiourea organocatalyst. Inspired by their earlier research on

parallel-turn linkers in un-natural foldamers,[91] the authors synthesised conformationally well-defined yet flexible thiourea catalyst **193**.



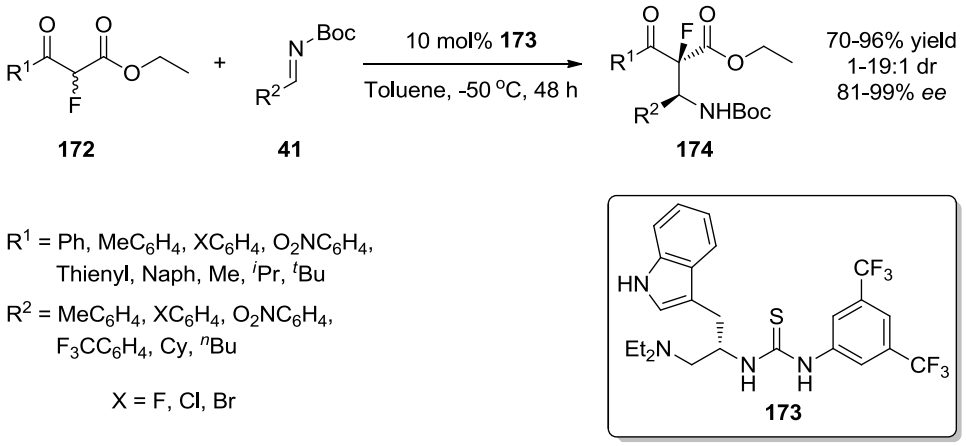
Scheme 55. Mannich reaction catalysed by conformationally well-defined thiourea

The authors then examined the Mannich reaction with silyl enolate **192** and found the catalyst to be highly enantioselective and high yielding (Scheme 55).[92] To confirm the catalyst's efficiency over catalysts not bearing the intra-molecular hydrogen bonding network, a competition experiment between catalysts **170** (known to generate (*S*)-**157**) and **171** (known to generate (*R*)-**157**) was initiated. It was found that when 1 mol% of each catalyst was used, Mannich product (*S*)-**157** was obtained in a 97% yield and with 93% *ee* (Scheme 56). This indicates that the intramolecular hydrogen bonding network of **170** has created a significantly more reactive catalyst for the reaction.



Scheme 56. Competition experiment for thiourea catalysed Mannich reaction

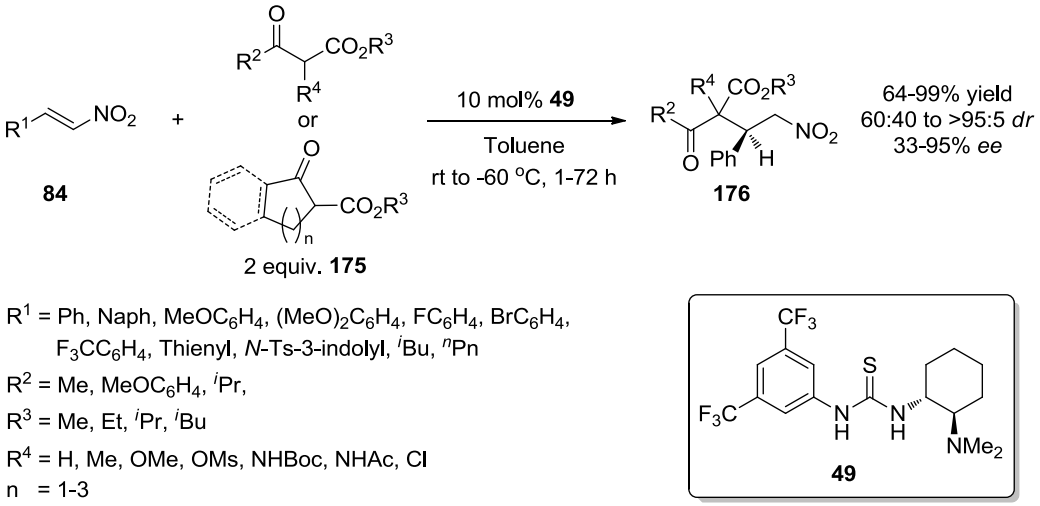
Huang and Lu's groups reported a Mannich reaction of fluorinated malonates **172** and *N*-Boc imines **41**. Attempts to use thioureas based on cinchona alkaloids such as those used by Dixon *et al.* (Scheme 52)[87] failed to give the desired products in high enantio- and diastereoselectivity. However, the authors found that thioureas based on amino acid tryptophan such as **173** could catalyse the reaction to give desired Mannich products **274** with excellent enantioselectivity (Scheme 57).[93]



Scheme 57. Asymmetric Mannich reaction of fluorinated ketoesters

1.3.4 Thiourea catalysed additions to nitroalkene electrophiles

Along with Jacobsen's early work on thiourea catalysed Strecker reactions, Takemoto's work on the additions of malonates to nitroalkenes greatly increased the interest in the field of thiourea organocatalysis.



Scheme 58. Expanded scope of thiourea catalysed nitro-Michael reactions

Further to their initial 2003 report, the group disclosed a report two years later with an improved substrate scope as well as experimental investigations into the mechanism

of the reaction (Scheme 58).[94] The authors were able to show that the reaction could form quaternary centres with high enantioselectivity, albeit with variable diastereoselectivity, as well as tolerate a variety of cyclic malonates. Kinetic studies showed that the reaction was first-order in nitroalkene, malonate and catalyst. Takemoto's group suggested a transition step similar to **TS-14** where the nitroalkene H-bonds to the thiourea moiety (Figure 10). However, computational studies by Pápai *et al.* suggest that the mechanism involves bonding of the malonate to the thiourea, rather than the nitroalkene, as depicted in **TS-15**.[95] The *R* enantiomer is proposed to be preferred over the *S* enantiomer in both mechanisms as this positions the substrates in a staggered conformation along the forming C-C bonds, thus minimising any steric interactions.

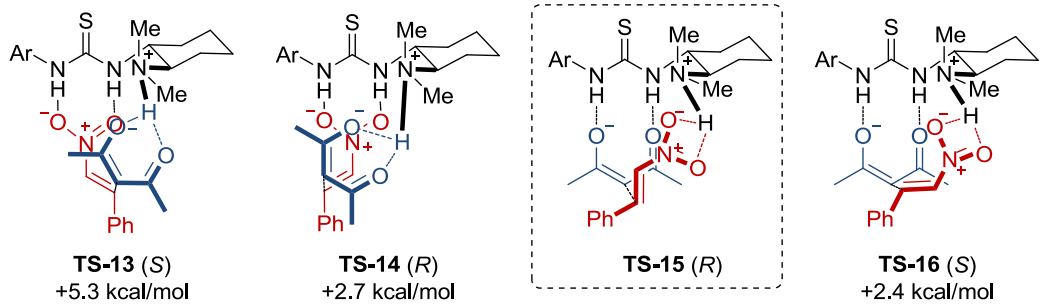
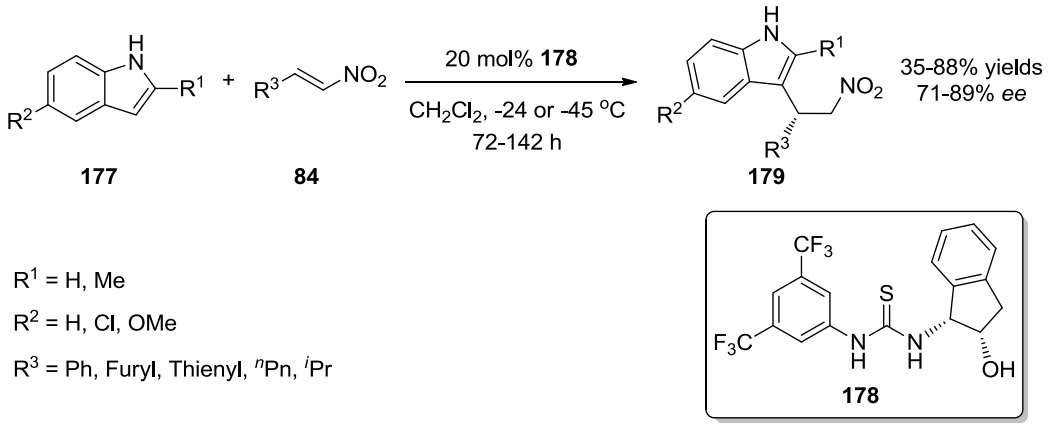


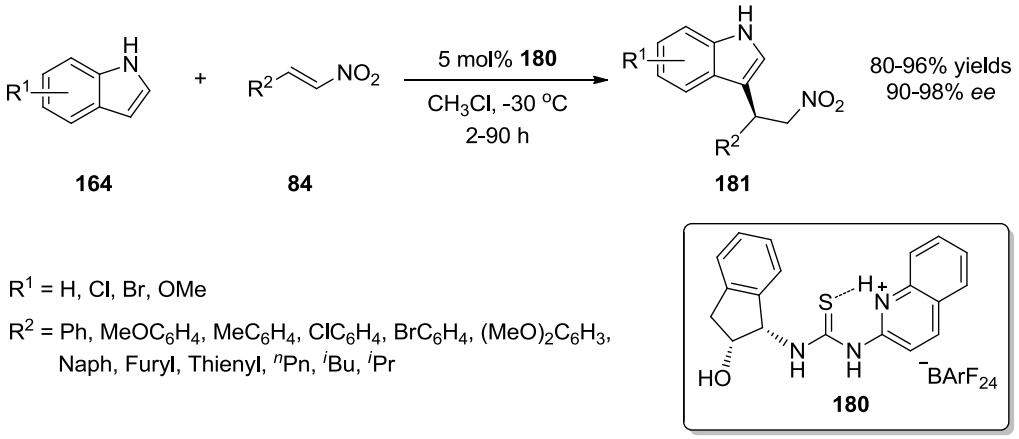
Figure 10. Possible transition states for thiourea catalysed nitro-Michael reaction

Since Takemoto's group published the first thiourea catalysed addition of malonates to nitroalkenes there have been a variety of other thiourea catalysts used to perform similar reactions such as those based on binapthalene scaffolds,[96] Cinchona alkaloids,[97] and those bearing multiple hydrogen bonding donors.[98]



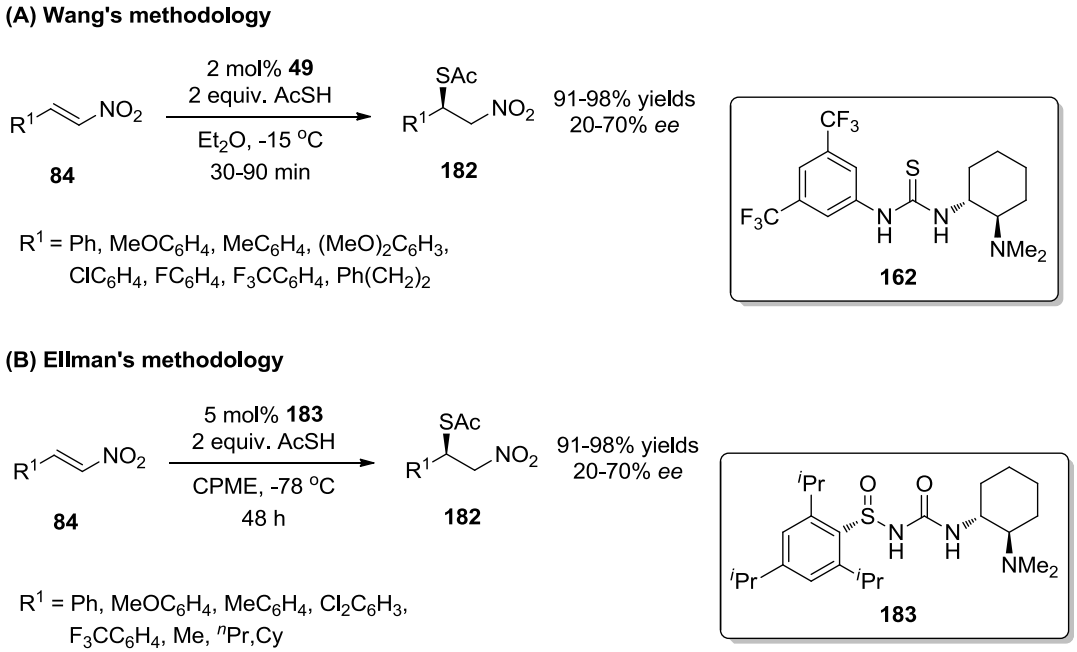
Scheme 59. Thiourea catalysed Friedel-Crafts reaction of indoles with nitroalkenes

In 2005, Ricci *et al.* reported an asymmetric Friedel-Crafts alkylation reaction of indoles **177** with nitroalkenes **84**. Using thiourea catalyst **178** the authors were able to obtain the desired products **179** in good enantioselectivity and moderate to high yields (Scheme 59).[99]



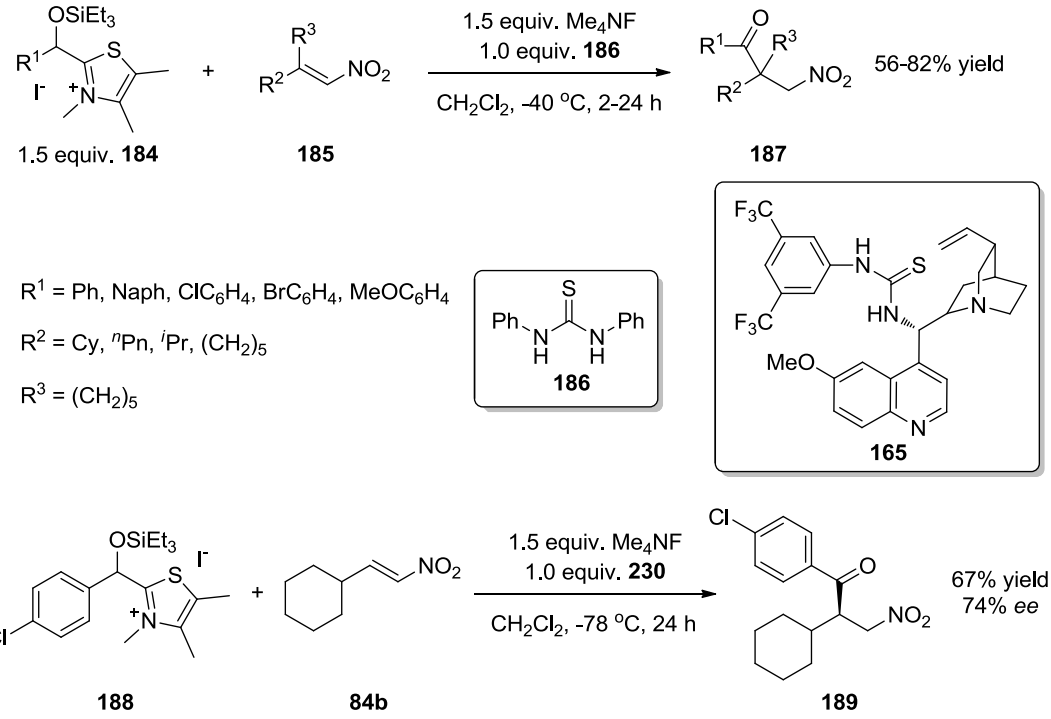
Scheme 60. Improved Friedel-Crafts reaction using a quinolinium containing thiourea

More recently, the group of Seidel have improved this reaction using a rationally designed quinolinium containing thiourea. The new catalyst greatly enhances the rate of reaction with the majority of reactions reaching completion within 24 h using only 5 mol% of catalyst **180** (Scheme 60).[100] The increased reactivity is attributed to the intramolecular H-bond between the sulfur and quinolinium species increasing the H-bond acidity of the catalyst.



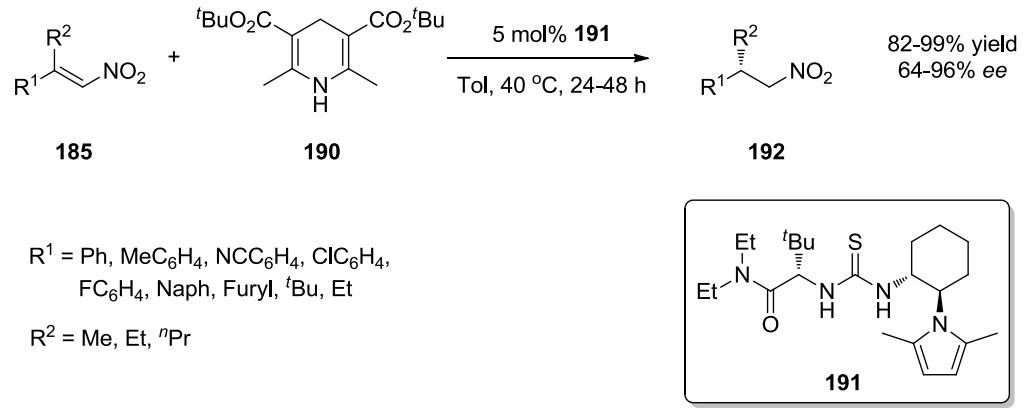
Scheme 61. (thio)urea catalysed additions of thioacetic acid to nitroalkenes

In 2006, Wang *et al.* applied Takemoto's catalyst **49** in the enantioselective addition of thioacetic acid to nitroalkenes **84**. Although, the reaction was high yielding the enantioselectivity was only moderate (Scheme 61, A), presumably due to competitive background reactions and retro-addition. In 2009, Ellman's group reported an improved procedure using urea catalyst **183** which resulted in significantly higher enantioselectivities albeit with lower yields and significantly longer reaction times (Scheme 61, B). The low temperature of -78 ^{o}C was required to prevent the background racemic reaction occurring.



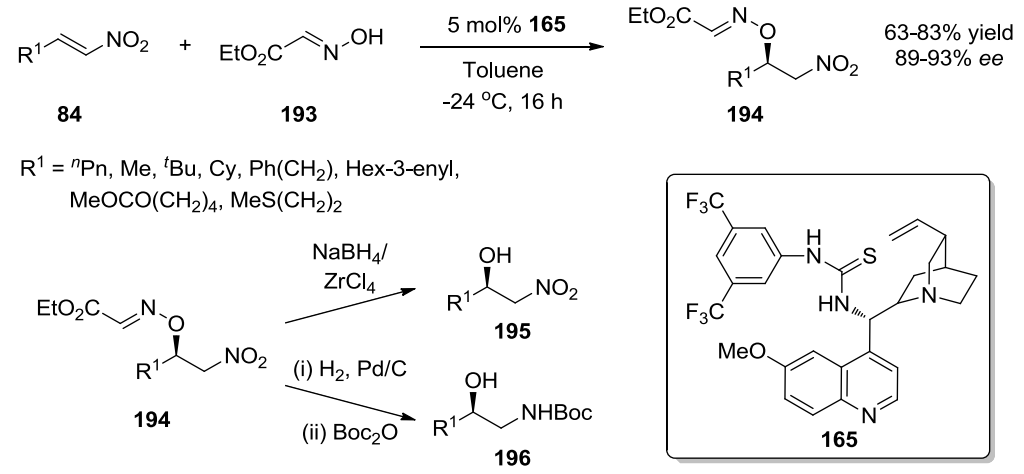
Scheme 62. Acylation of nitroalkenes promoted by a thiourea/fluoride anion combination

Also in 2006, Scheidt's group reported a direct acylation of nitroalkenes promoted by a thiourea/ fluoride anion combination.[101] Using a mixture of triethylsilyl thiozolium carbinol **184**, tetramethylammonium fluoride and thiourea **186** desired *β*-nitro ketones **187** could be formed in good yields (Scheme 62). Without the addition of the thiourea the reaction yields were approximately half of those obtained with the dual activation strategy. An asymmetric reaction was also attempted using cinchona-alkaloid derived thiourea **165** which gave *β*-nitro ketone **189** in a 67% yield and in 74% *ee* (Scheme 62). However, no catalytic variant has been reported since.



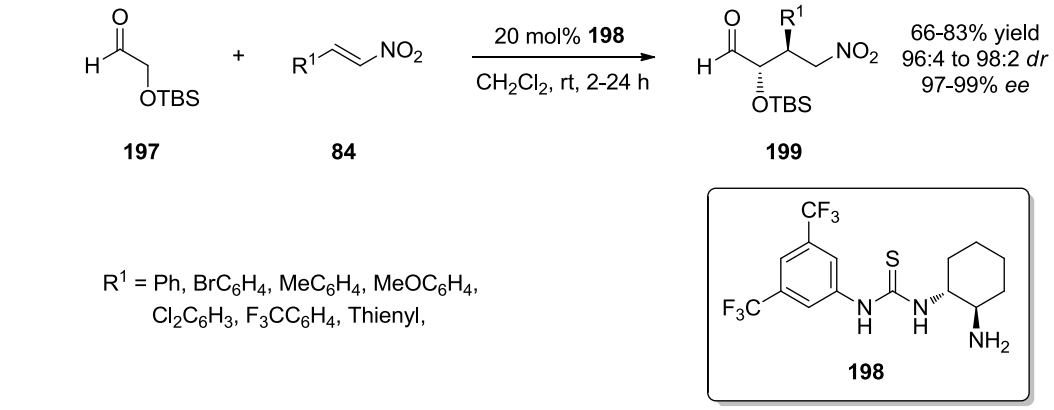
Scheme 63. Thiourea catalysed reduction of nitroalkenes

In the same year List's group disclosed an asymmetric transfer hydrogenation of nitroalkenes.[102] Using thiourea **191** and Hantzsch ester **190** as an NADPH mimic, the authors could efficiently reduce a variety of *α*-alkyl-*β*-nitrostyrenes **185** with high degrees of stereocontrol (Scheme 63). The authors have since extended their methodology to include *β*-nitroacrylates,[103] and a number of similar reports have appeared, although these fail to match the results of the original procedure.[104]



Scheme 64. Enantioselective hydroxylation of nitroalkenes using thiourea catalysis

Jørgensen *et al.* reported an enantioselective hydroxylation of nitroalkenes using oxime **193** as a "masked" water molecule.[105] Using thiourea catalyst **165** the authors were able to form a variety of *β*-nitro oximes **194** in good yields and high enantioselectivity (Scheme 64), which could be simply reduced to give *β*-nitroalcohols **195** or 1,2-aminoalcohols **196**.



Scheme 65. Thiourea catalysed *anti*-selective nitro-Michael reaction

In 2009, the group of Barbas III published an *anti* selective asymmetric nitro-Michael reaction using thiourea **198**.[106] Using (*tert*-butyldimethylsilyloxy)acetaldehyde **197** as the nucleophile the authors could react a variety of nitroalkenes to form desired products **199** in good yields and with excellent stereoselectivity (Scheme 65). Using standard proline catalysis the reaction favours the *syn* diastereomer due to acyclic synclinal transition state **TS-17** where the more stable *E* enamine is the reactive species. However, using catalysts with primary amines such as thiourea **198** the reaction forms the *anti* diastereomer as it is proposed that the *Z* enamine is the reactive species in transition state **TS-18** (Figure 11).

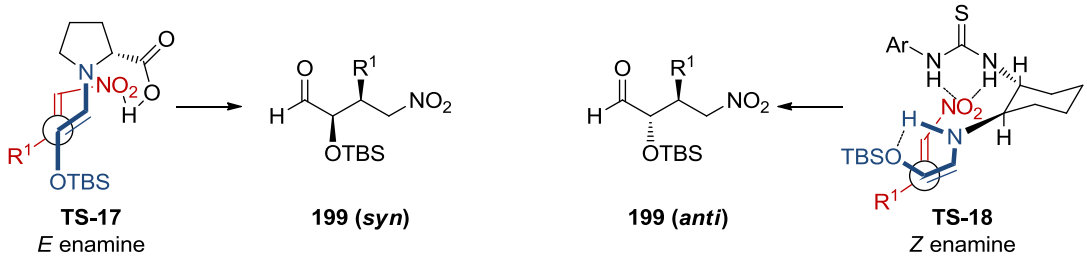
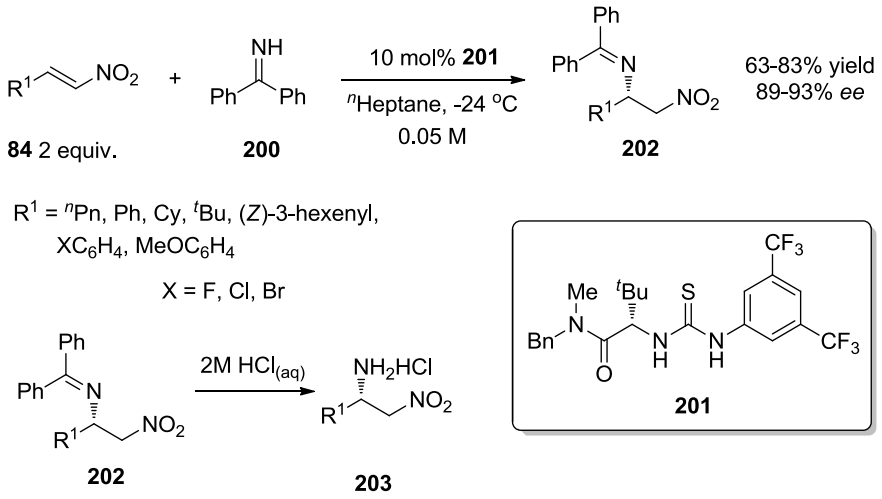


Figure 11. Transition states for *syn* and *anti* selective nitro-Michael reactions

In 2010, Jørgensen's group, inspired by the use of imines as ammonia equivalents in Buchwald-Hartwig couplings,[107] developed a thiourea catalysed aza-nitro-Michael reaction.[108] Using thiourea **201** the authors were able to add ketimines **200** into a variety of nitroalkenes **84** with good levels of enantioselectivity and high yields. The protecting group could be easily removed from products **202** under acidic aqueous conditions to give amine hydrochloride salt **203** (Scheme 66).



Scheme 66. Thiourea catalysed aza-nitro-Michael reaction of imines

Interestingly, the authors observed an inversion of stereochemistry when using molecular sieves prompting them to hypothesise the possible involvement of water in the transition state of the reaction (Figure 12). In the absence of water the highlighted C-H bond sits in the same plane as the C=S bond resulting in blocking of the bottom face by the large *tert*-butyl group as shown in transition state **TS-20** resulting in formation of the *R* enantiomer.

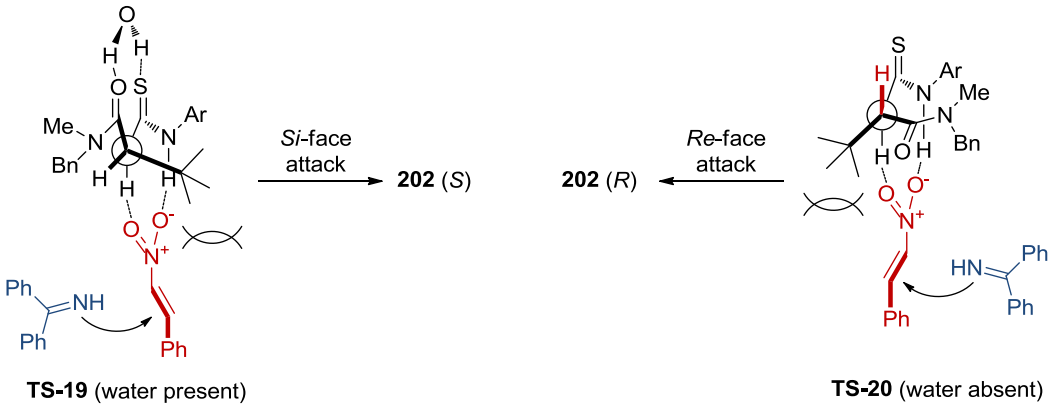
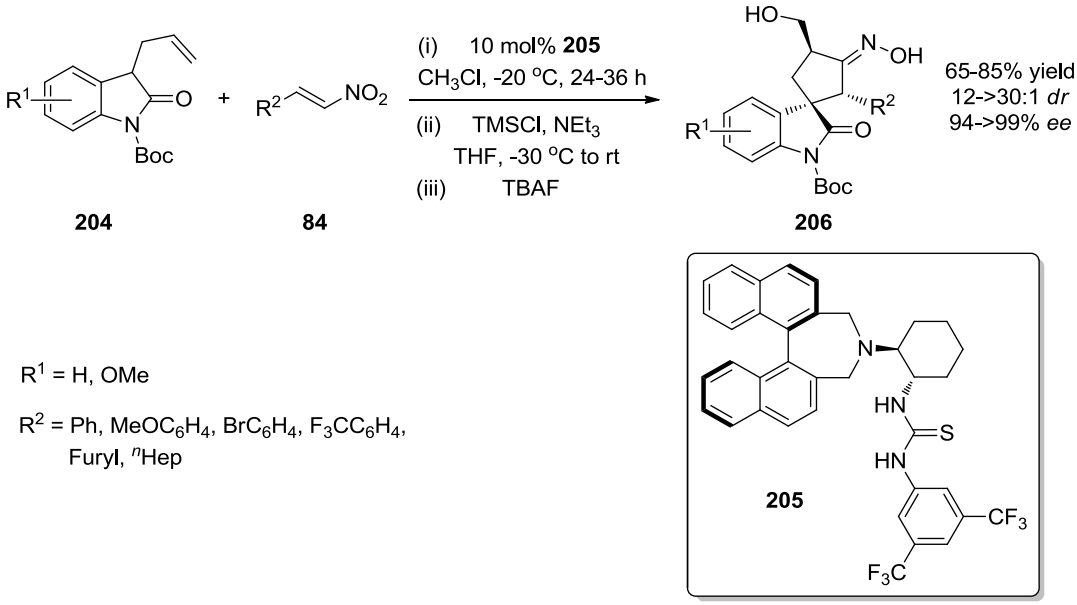


Figure 12. Proposed transition states for aza-nitro-Michael reaction

In the presence of water, a bridging interaction between water, the carbonyl and thiocarbonyl could give intriguing transition state **TS-19**, which increases rigidity in the catalyst, leading to the observed *S* enantiomer of **202**. The authors referenced water induced conformational changes in peptide-like structures as support for their proposed transition state.[109]

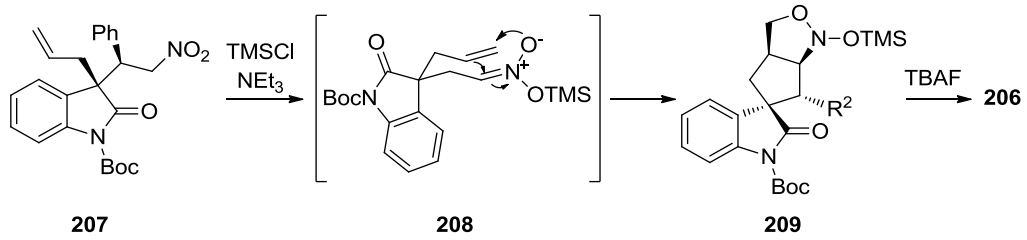
In 2011, Shao's group disclosed a highly enantioselective one-pot synthesis of spirocyclopentaneoxindoles **206** using thiourea **205**.[110] Using a combination of

oxindoles **204**, nitroalkenes **84**, TMSCl and then tetrabutylammonium fluoride (TBAF) the authors could form complex spirocycle products **206** containing three stereocentres in high yields and excellent stereoselectivity (Scheme 67).



Scheme 67. One-pot synthesis of spirocyclopentaneoxindoles using thiourea catalysis

The reaction proceeds *via* a nitro-Michael reaction to give **207**, which is then turned into silyl-nitronate **208** which undergoes an intra-molecular silyl nitronate-olefin cycloaddition to form **209**. Upon addition of TBAF, isoxazolidine **209** fragments to form desired spirocycle **206** (Scheme 68).

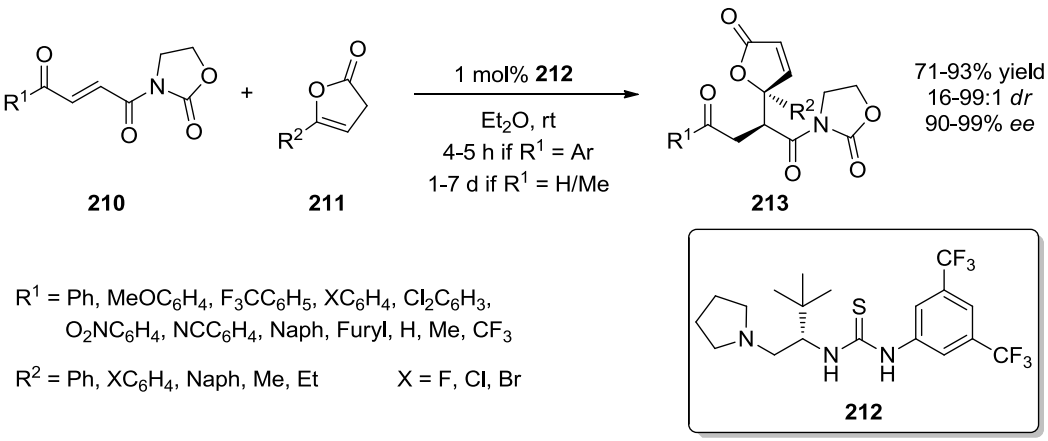


Scheme 68. Mechanism of spirocyclopentaneoxindole formation

1.3.5 Thiourea catalysed additions to other electrophiles

As well as imines and nitroalkenes, a number of reports of thiourea catalysed reactions such as additions to various Michael acceptors, 1,2 additions to carbonyls, anion recognition, kinetic resolutions and desymmetrisation reactions have been reported.[73] Due to the large amount of research performed in this area, this section will only briefly detail some representative examples that are deemed noteworthy due

to their high levels of stereocontrol and complexity or the use of novel innovative catalysts.



Scheme 69. Thiourea catalysed conjugate addition of *γ*-substituted butenolides

Recently, the groups of Huang, Tan and Jiang have reported a highly enantio- and diastereoselective vinylogous conjugate addition of *γ*-substituted butenolides **210** (Scheme 69).[111] Using only 1 mol% of thiourea **212** the authors were able to form desired products **213** with excellent levels of stereo- and chemoselectivity. The authors also performed some density functional theory (DFT) calculations to calculate the transition state for the enantiodetermining step. It was found that for the lowest energy transition state a crucial non-classical C-H···O hydrogen bond between the *α*-H of the pyrrolium moiety and the oxazolidinone C=O bond was present (Figure 13).

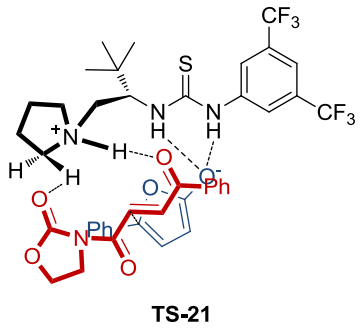
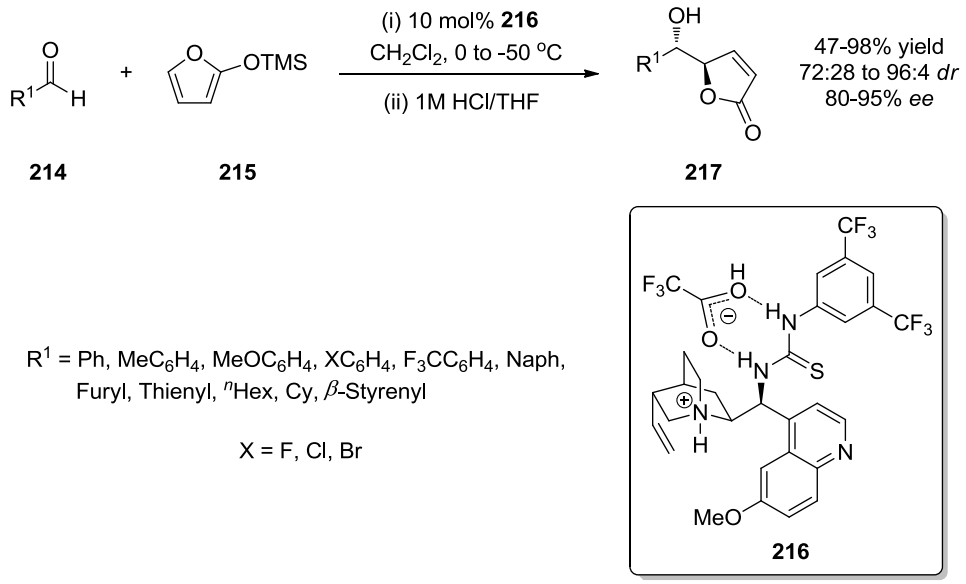


Figure 13. Proposed transition state for conjugate addition of *γ*-substituted butenolides

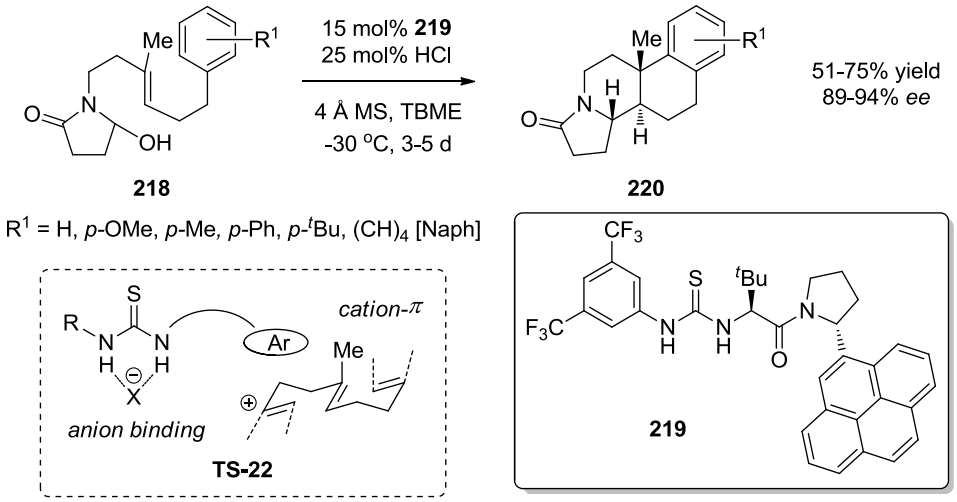
In 2010, Deng and co-workers reported an asymmetric vinylogous aldol reaction of siloxy furan **215** using thiourea containing chiral salt **216** giving rise to desired products **217** in excellent yields and stereoselectivitity (Scheme 70).[112] The authors had recently determined the structure of chiral salt **216** by X-ray crystallography. They envisaged a possible catalytic cycle, whereby the Hydrogen-bonded carboxylate

could react with siloxy furan **215** to form the 2-furoxy anion and trimethylsilylester. This anion could then undergo the desired reaction under catalyst control.



Scheme 70. Asymmetric vinylogous aldol reaction of siloxy furans using a chiral salt

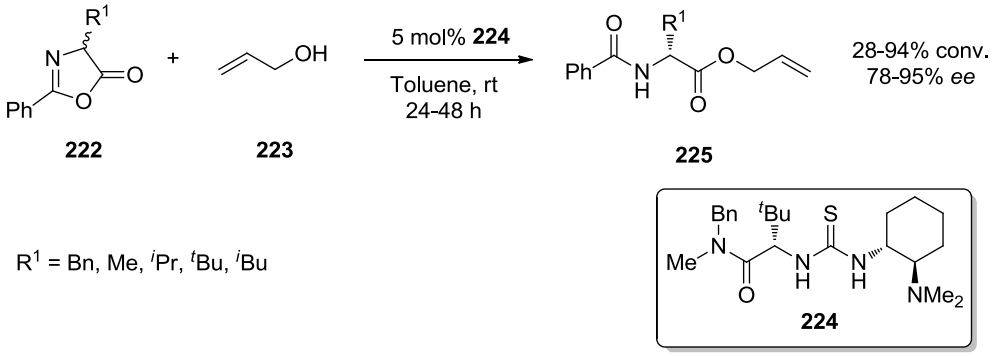
There have also been a number of reports detailing the use of thioureas as anion abstractors to generate highly reactive cationic intermediates.[113] One such example was reported by Jacobsen *et al.* in 2010 detailing thiourea catalysed polycyclisations.[114] Using thiourea **219** the authors were able to perform a bicyclisation of hydroxylactams **218** to form tetracycles **220** in good yield and with excellent enantioselectivity (Scheme 71).



Scheme 71. Enantioselective thiourea-catalysed cationic polycyclisation

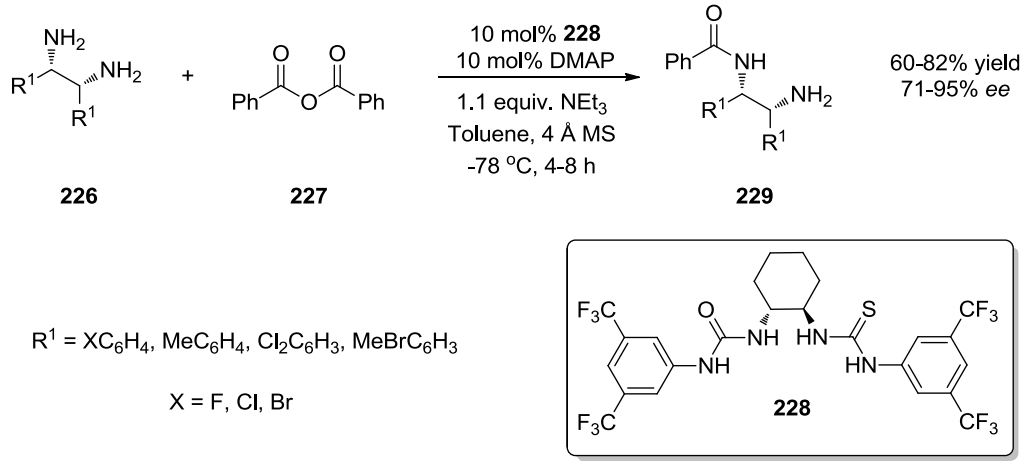
It was proposed that there was a cation-π interaction between the large arene ring and the cationic *N*-acyliminium species giving rise to high levels of stereocontrol. This

was supported by a decrease in enantioselectivity when using smaller polyarenes which correlated strongly with the polarisability and quadropole moments of the arenes.



Scheme 72. Enantioselective dynamic kinetic resolution using thiourea catalysis

In 2005, Berkessel's group disclosed the first example of a thiourea-based dynamic kinetic resolution of azlactones,[115] as a means to produce enantioenriched un-natural amino acids. Using thiourea **224** and allyl alcohol **223**, a range of racemic azlactones **222** could be converted into *N*-benzoylamino acid allyl esters **225** in high enantiomeric excess (Scheme 72).



Scheme 73. Catalytic enantioselective desymmetrisation of *meso*-diamines

A final use of thiourea catalysts has been in desymmetrisation reactions. Seidel *et al.* reported the use of thiourea **228** in the desymmetrisation of *meso*-diamines **226** (Scheme 73).[116] When combined with 4-dimethylaminopyridine, thiourea **228** and benzoic anhydride **227** form a chiral ion pair which can control the enantiospecificity of the subsequent amide formation. The same strategy has also been applied to the kinetic resolution of amines.[117]

1.4 Proposed research

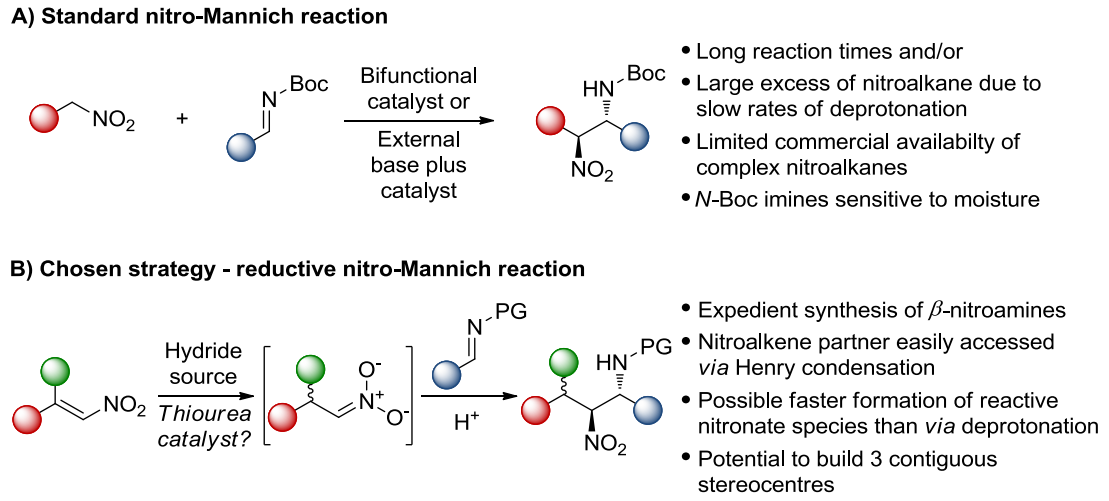
1.4.1 Overview and limitations of the nitro-Mannich reaction

As has been shown in the previous sections, the nitro-Mannich reaction is a powerful carbon-carbon bond forming reaction. The products obtained from the reaction are also particularly useful as they contain two nitrogen groups in distinct oxidation states allowing for complete chemoselectivity in subsequent reactions. However, despite the advances observed in the chemistry of the nitro-Mannich reaction over the past thirteen years, some problems still exist (Scheme 74, A).

- The scope of the reaction with respect to the nitroalkane substrate has still not been fully explored with the majority of reports only examining common commercially available nitroalkanes such as nitromethane, nitroethane and nitropropane.
- Nitroalkanes are often used in a large excess (typically 5 to 10 equivalents) or long reaction times are required due to slow rates of reaction.
- Formation of the reactive nitronate species requires either an extra synthetic step, to form a more stable nitronate as in the case of silyl-nitronates; the addition of an external base to deprotonate the nitroalkane, which reduces the atom efficiency of the reaction; or the use of a much more complex bifunctional catalyst containing basic and acidic functionalities, which are often much more expensive to buy or synthesise.
- The majority of current syntheses use *N*-Boc protected imines which are inherently moisture sensitive, often requiring the addition of molecular sieves.
- The nitro-Mannich reaction has limited reactivity with ketimines rendering it difficult to produce products possessing a quaternary centre.

1.4.2 Chosen strategy

We hoped to overcome some of, if not all of these problems by applying a reductive strategy, whereby addition of a hydride nucleophile to a nitroalkene should form the reactive nitronate species which can then undergo an *in situ* nitro-Mannich reaction with an imine (Scheme 74, B).

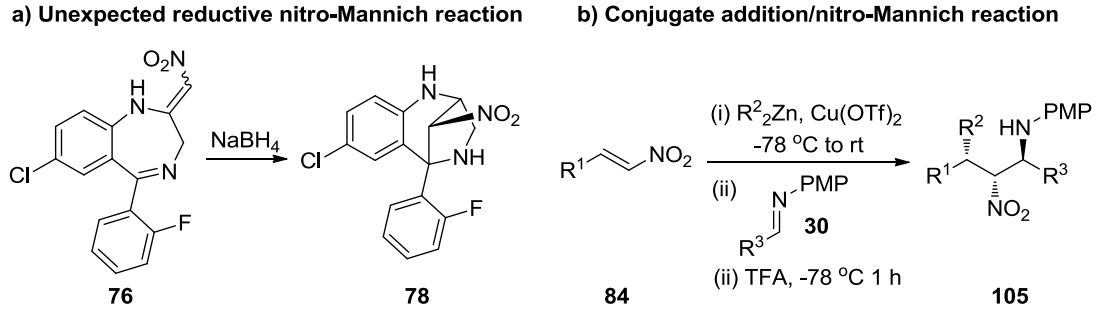


Scheme 74. Comparison of current nitro-Mannich procedures with proposed research

Using such a strategy would enable the use of more complex nitroalkene starting materials, many of which are commercially available or can be readily accessed *via* an Henry condensation reaction. The synthesis of complex nitroalkanes, required for the standard nitro-Mannich reaction, would most likely originate from the corresponding nitroalkene. Hence the one-pot reductive strategy is more a more efficient route to *β*-nitroamines. In addition, such a strategy has the potential to build three contiguous stereocentres enabling rapid formation of complex molecular architectures. Forming the reactive nitronate species *via* addition of a hydride nucleophile rather than *via* deprotonation may also result in a significantly faster rate of reaction and therefore require less equivalents of the nitro-partner than in "standard" procedures. Such a rapid formation of the nitronate may also lead to better reactivity with ketimines.

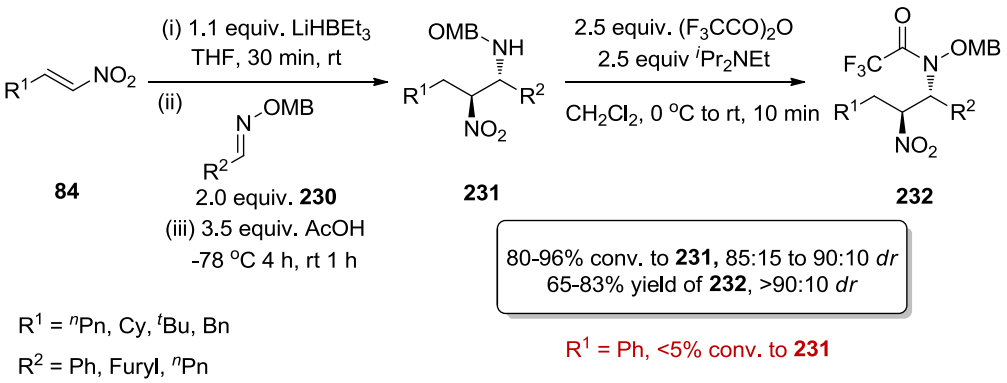
1.4.3 Precedent for a racemic reductive nitro-Mannich reaction

There is some literature precedent for a racemic reductive nitro-Mannich reaction, as was detailed in section 1.1.7, scheme 27. An unexpected intramolecular nitro-Mannich reaction has been observed previously upon addition of sodium borohydride to a nitroalkene compound containing an imine.[46]



Scheme 75. Literature precedent for a general reductive nitro-Mannich reaction

Additionally, the Anderson group have recently reported a conjugate addition/nitro-Mannich reaction. In these systems the reactive nitronate species is accessed *via* addition of dialkyl zinc, in a similar fashion to our proposed hydride addition, before an *in situ* nitro-Mannich reaction with an imine ensues (section 1.1.7, Scheme 33).[53] Both of these reactions are summarised in scheme 75.

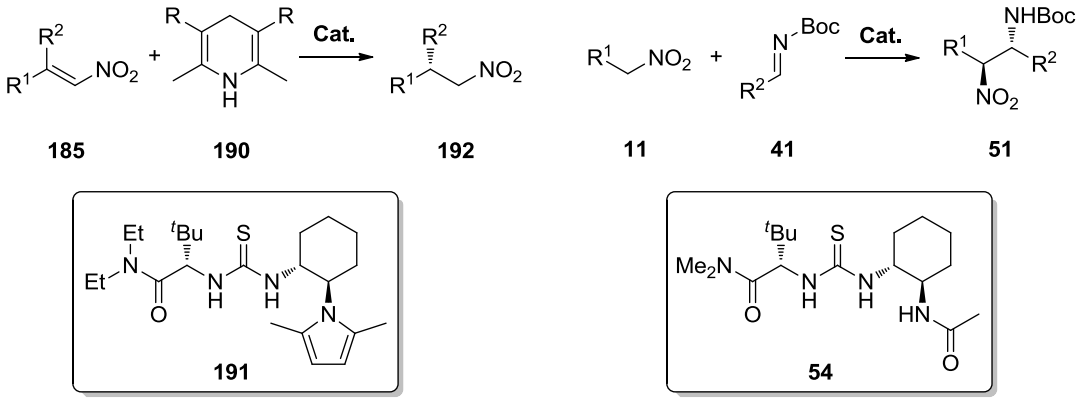


Scheme 76. Previous work on the reductive nitro-Mannich reaction

Preliminary work in the Anderson group by G. Stepney began to examine the potential of a general reductive nitro-Mannich reaction.[118] It was found that by using a reductant with a precise hydride stoichiometry, such as Superhydride™ (lithium triethylborohydride), a selective conjugate reduction of nitroalkenes **84** could be performed. Subsequent cooling to -78 °C and addition of *ortho*-methoxybenzyl (OMB) imine **230** followed by acetic acid formed desired *β*-nitroamines **231**. However, the reaction was only successful when using aliphatic nitroalkenes. No reactivity was observed with nitrostyrenes and the scope of the reaction with respect to different imines was never fully explored (Scheme 76).

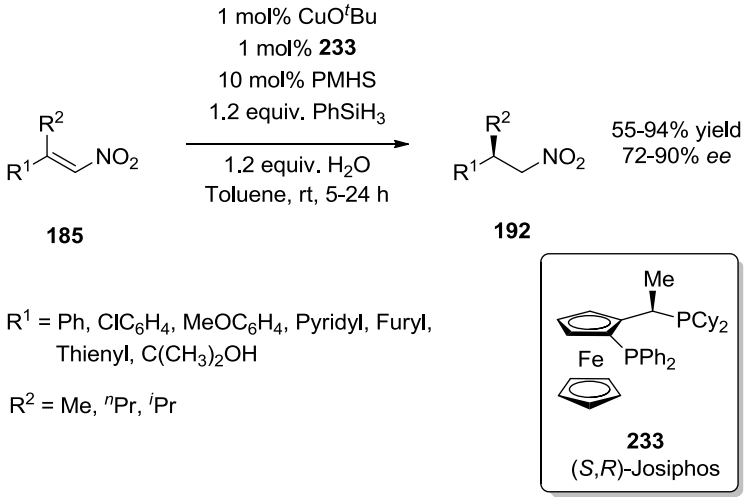
1.4.4 Precedent for an asymmetric reductive nitro-Mannich reaction

Further to this there are several reports that suggested potential for an asymmetric variant of a reductive nitro-Mannich reaction. One such method would be to use thiourea organocatalysis which has been previously shown to catalyse both reductions of nitroalkenes (see section 1.3.4, Scheme 63) and nitro-Mannich reactions (section 1.1.5).



Scheme 77. Literature precedent for an asymmetric reductive nitro-Mannich reaction

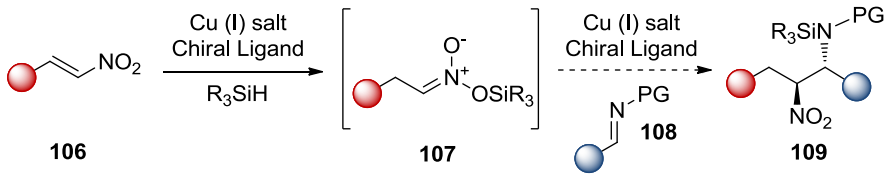
Given the similarities of the catalysts it is reasonable to assume that a reaction performing both transformations should be possible. However, there may be some compatibility issues with regards to the reduction which may favour reduction of the imine over the nitroalkene.



Scheme 78. Copper hydride asymmetric reduction of nitroalkenes

If such a strategy was unsuccessful, it may also be possible to perform the reaction using copper hydride chemistry. Carreira *et al.* have reported the asymmetric reduction of nitroalkenes **185** using chiral phosphine ligand **233** and a mixture of

phenylsilane and polymethylhydrosiloxane (PMHS) as the hydride source (Scheme 78).[119] The authors later reported two improved procedures, one using an alternative more air stable copper source,[120] the second allowing reduction of an isomeric mixture of nitroalkenes.[121] Presumably, such a reaction would form a silyl nitronate species. Given that the Anderson and Jørgensen groups have both reported copper catalysed nitro-Mannich reactions of silyl nitronates, combining these two methodologies seems plausible (Scheme 79). In addition to this, for the other members of the nitro-Mannich reaction family; enantioselective reductive aldol,[122] and Mannich reactions have been previously reported.[123] A racemic reductive Henry reaction has also been disclosed using copper hydride.[124]



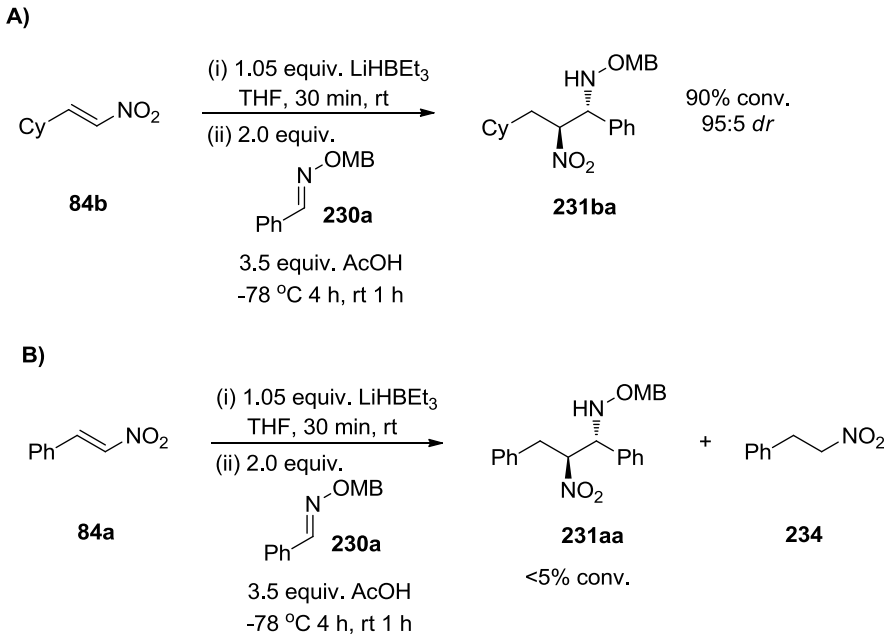
Scheme 79. Proposed copper catalysed reductive nitro-Mannich reaction

Chapter 2. Results and discussion

2.1 The racemic reductive nitro-Mannich reaction

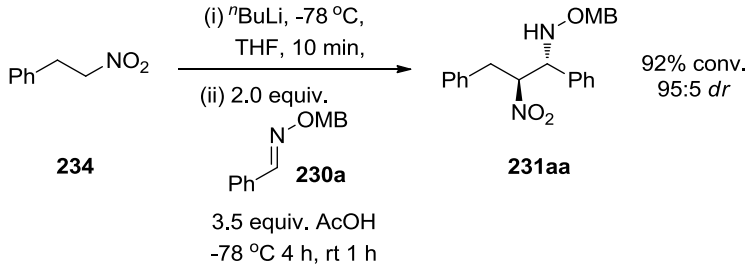
2.1.1 Initial investigations

As was stated in section 1.4.3, a previous member of the group had conducted investigations into a racemic reductive nitro-Mannich.[118] It was discovered that using Superhydride™ as a reductant followed by addition of an *N*-OMB imine and acetic acid at -78 °C would form the desired products. However, the reaction was only successful for aliphatic nitroalkenes with no conversion to the desired product observed when using *β*-nitrostyrene. Consequently, initial investigations were aimed at solving this problem. The previous researcher, G. Stepney, had performed some additional experiments aiming to identify the cause of the intolerance of nitrostyrenes. Scheme 80 shows the reactions using cyclohexyl nitroalkene **84b** (A) and *β*-nitrostyrene **84a** (B). Full reduction of the nitrostyrene occurred suggesting that the nitro-Mannich reaction was unable to proceed.



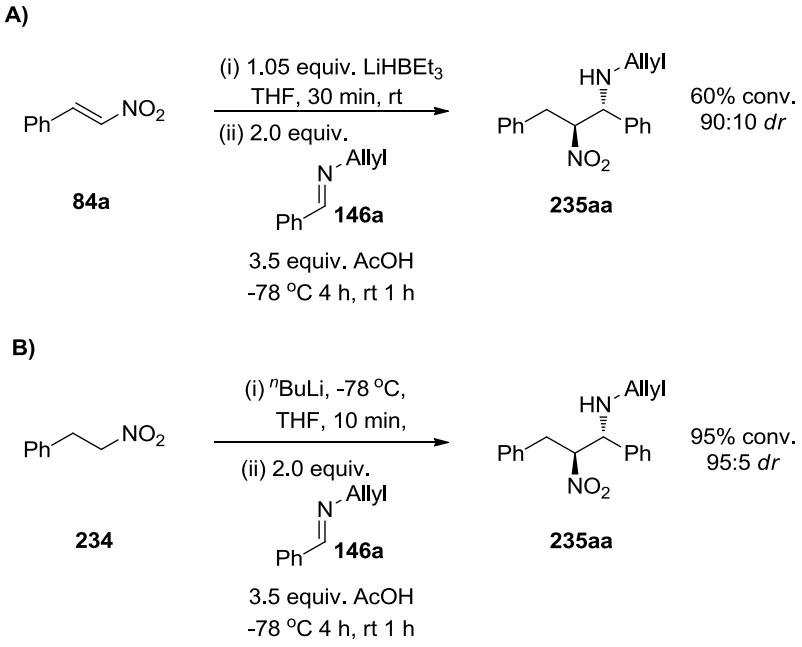
Scheme 80. Comparing aliphatic and aromatic nitroalkenes under reaction conditions

Subsequently, G. Stepney examined the ability of nitroalkane **234** to undergo a standard nitro-Mannich reaction by deprotonation with ^{n}BuLi. This was successful, achieving greater than 90% conversion to desired *β*-nitroamine **231aa** with a 95:5 diastereomeric ratio (Scheme 81).



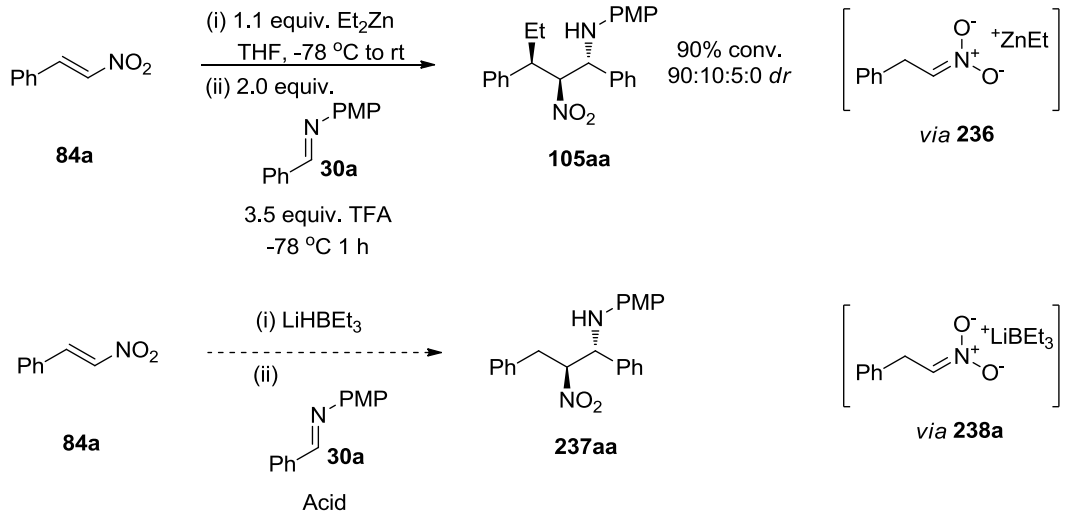
Scheme 81. Standard deprotonation nitro-Mannich reaction of nitroalkane **234**

The success of this reaction suggested that the presence of triethylborane may be responsible for the lack of reactivity of nitrostyrene **84a** in the reductive nitro-Mannich reaction. However, further experiments performed by G. Stepney proved inconclusive as it was found that allyl protected imine **146a** could promote the desired reductive nitro-Mannich reaction albeit with a lower yield than *via* a standard deprotonation strategy (Scheme 82).



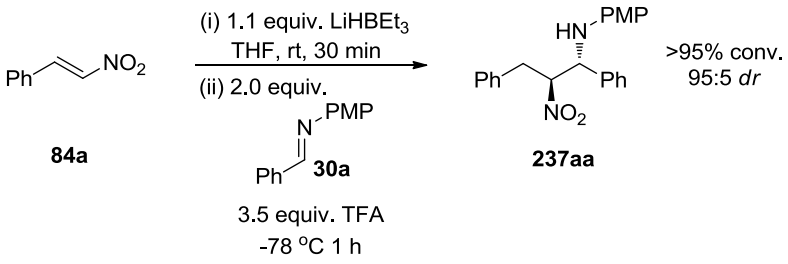
Scheme 82. Comparing reductive and deprotonation strategy for *n*-allyl imine **146a**

These experiments pointed to there being a combination of factors preventing a successful reaction occurring when using *N*-OMB imine **230a** with nitroalkene **84a**. In addition to the work on the reductive nitro-Mannich reaction other recent work in the Anderson group has examined a conjugate addition/nitro-Mannich reaction using diethyl zinc (see section 1.1.7, Scheme 33) which used *N*-PMP imines **30**.



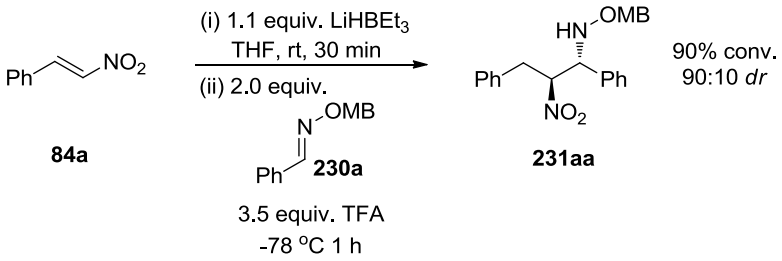
Scheme 83. Use of *N*-PMP imines in the nitro-Mannich reaction

This reaction was successful when using nitrostyrenes, although the nitronate formed from such a reaction would be different to the nitronate arising from hydride addition, this seemed like a good place to start our new investigations (Scheme 83). It should be noted that trifluoroacetic acid was used to activate the less basic *N*-PMP imine **30** (compared to the use of acetic acid with more basic *N*-OMB imine **230**).



Scheme 84. Reductive nitro-Mannich reaction using *N*-PMP imine **30a**

With this knowledge in hand, the reductive nitro-Mannich reaction was first performed on *β*-nitrostyrene **84a** using *N*-PMP protected imine **30a**. Pleasingly the reaction proceeded to give desired *β*-nitroamine **237aa** in high diastereoselectivity (*dr* - 95:5) and quantitative conversion (Scheme 84). Although this was a pleasing result it did not help to explain the poor reactivity of *N*-OMB imine **230a**. To further probe this reaction and explain why the reaction with *N*-OMB imine **230a** and *β*-nitrostyrene **84a** did not work more experiments were performed. Surprisingly, the reaction between *β*-nitrostyrene **84a**, *N*-OMB protected imine **230a** and trifluoroacetic acid was successful (Scheme 85).



Scheme 85. Reaction of *N*-OMB imine **230a** using trifluoroacetic acid

Interestingly, it was observed that the resultant nitronate **238a** from the reduction of **84a** with Superhydride™ was insoluble in the reaction solvent. It could even be isolated as a white solid. However, when TFA was added to this heterogeneous mixture the nitronate species dissolves, but with acetic acid the precipitate remains. The analogous aliphatic nitronate **238b** was much more soluble in the reaction solvent and the reaction mixtures became completely homogenous on addition of TFA or acetic acid (Figure 14).

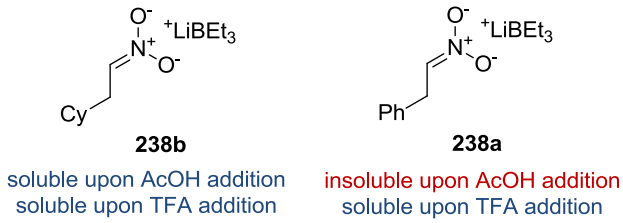
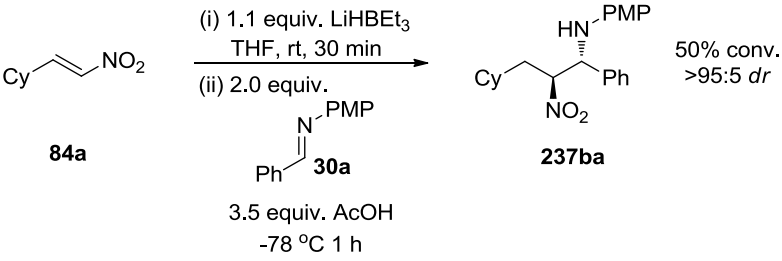


Figure 14. Solubilities of nitronates upon addition of acid

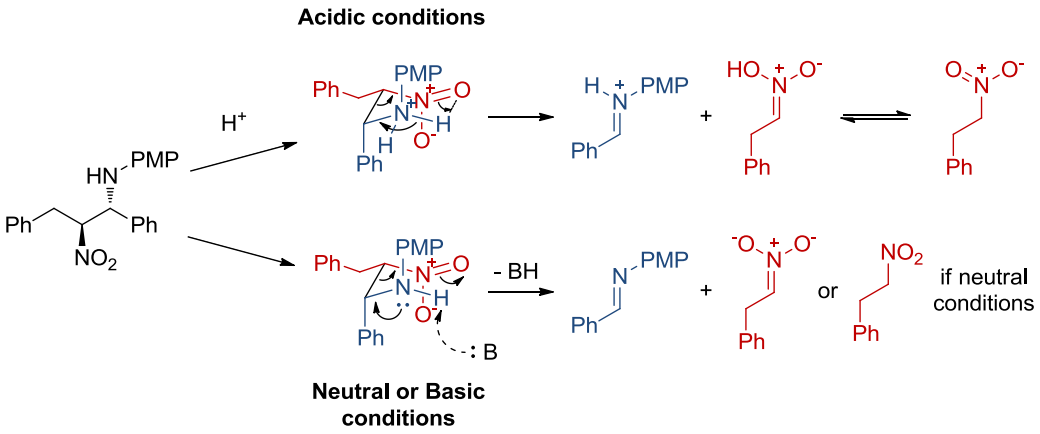
A final experiment using aliphatic nitroalkene **84b** and *N*-PMP imine **30a** with acetic acid gave the desired product with 50% conversion as a single diastereomer (Scheme 86).



Scheme 86. Reaction of an aliphatic nitroalkene with *N*-PMP imine using acetic acid

The difference in conversion between *N*-PMP imine **30a** and *N*-OMB imine **230a** may be due to the reduced basicity of the *N*-PMP imine **30a** slowing the rate of protonation with AcOH. In summation, the evidence described above seems to suggest that in order for the reductive nitro-Mannich reaction to proceed with good

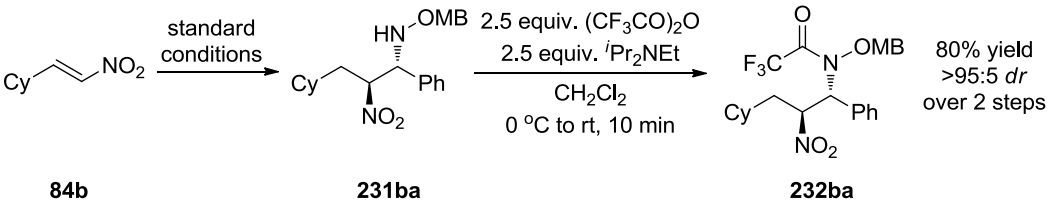
conversion, the nitronate must dissolve upon addition of an acid. Trifluoroacetic acid probably works well as not only is it strongly acidic (pK_a = -1) but the trifluoro group helps to solubilise the precipitates. The choice of imine is also evidently important as when using *N*-allyl imine **146a** some desired nitro-Mannich product was observed even when using acetic acid (Scheme 82). It is possible that the acid first protonates the imine and it is the solubilising effect of this protonated iminium species on the nitronate that is crucial. This could again explain the crucial role of trifluoroacetic acid as when protonating an imine this would form an iminium species with a highly solubilising trifluoroacetate counter ion.



Scheme 87. Degradation of nitro-Mannich products *via* retro-addition

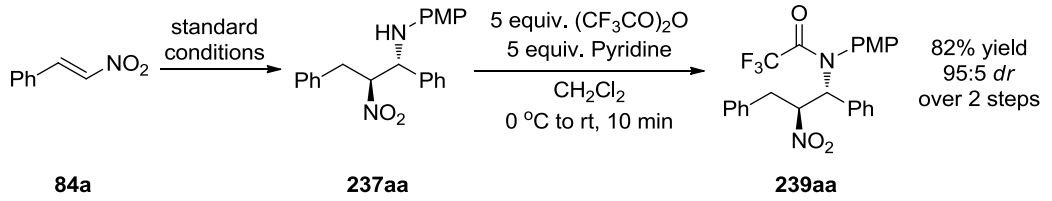
As with many nitro-Mannich reactions the products were unstable to purification by standard chromatographic methods (silica, neutral and basic alumina) and also only bench stable for a short while, with retro-addition products observed after approximately 24 hours. This reverse reaction could be acid promoted as well as occurring under neutral or basic conditions (Scheme 87). Theoretically, loss of diastereoselectivity could also be observed under strongly basic conditions due to epimerisation. In order to prevent the retro-addition and isolate the desired nitro-Mannich products, additional derivatisation of the amino functionality was required. Previous work in the Anderson group has used various reduction conditions to form 1,2-diamines, however these are also often unstable and require further derivatisation to make bench stable. A protection of the *β*-nitroamine would be a more preferable strategy. Fortunately, G. Stepney was able to show that *N*-OMB *β*-nitroamines **231** could be protected as trifluoroacetamides **232** using trifluoroacetic anhydride and Hunig's base (Scheme 88).[118] Other standard nitrogen protecting

group strategies such as employing Boc, tosyl or acetyl groups failed to form the desired products.[125]



Scheme 88. Trifluoroacetate protection of *N*-OMB nitro-Mannich product

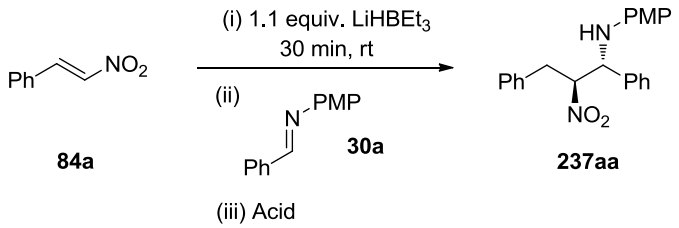
Pleasingly, a similar protection could be performed on *N*-PMP *β*-nitroamine **237aa** giving trifluoroacetamide **239aa** in an 82% yield in high diastereomeric purity (Scheme 89). Using only 2.5 equivalents of anhydride and base did not lead to full conversion to the desired trifluoroacetamide and some retro-addition was observed. However, a large excess (5 equivalents) of anhydride and base allowed the formation of the desired trifluoroacetamide before retro-addition could take place. Pyridine was used instead of Hunig's base to avoid formation of an unexpected by-product that had been observed during previous work.[118]



Scheme 89. Trifluoroacetate protection of *N*-PMP nitro-Mannich products

The conditions for the reductive nitro-Mannich reaction were then optimised (Table 1). It was discovered that the amount of imine could be reduced to 1.1 equivalents without having a detrimental effect on the reaction conversion and this also slightly increased the diastereoselectivity (Table 1, entry 2).

Table 1. Optimisation of reductive nitro-Mannich reaction with *N*-PMP-imines



Entry	N° equiv. imine	Acid (N° equiv.)	Solvent	Reaction temp. and time	% Conv.[a]	*dr*[b]
1	2.0	TFA (3.5)	THF	-78 °C 1 h, rt 1 h	>95	95:5
2	1.1	TFA (2.5)	THF	-78 °C 1 h, rt 1 h	>95	>95:5
3	1.1	TFA (2.5)	DCM	-78 °C 1 h, rt 1 h	>95	>95:5
4	1.1	TFA (2.5)	Et_2O	-78 °C 1 h, rt 1 h	>95	>95:5
5	1.1	TFA (2.0)	THF	-78 °C 1 h, rt 1 h	>95	90:10
6	1.1	TFA (1.0)	THF	-78 °C 1 h, rt 1 h	80	90:10
7	1.1	AcOH (2.5)	THF	-78 °C 1 h, rt 1 h	<5	n/a
8	1.1	TFA (2.5)	THF	-78 °C 1 h, rt 5 min	>95	>95:5

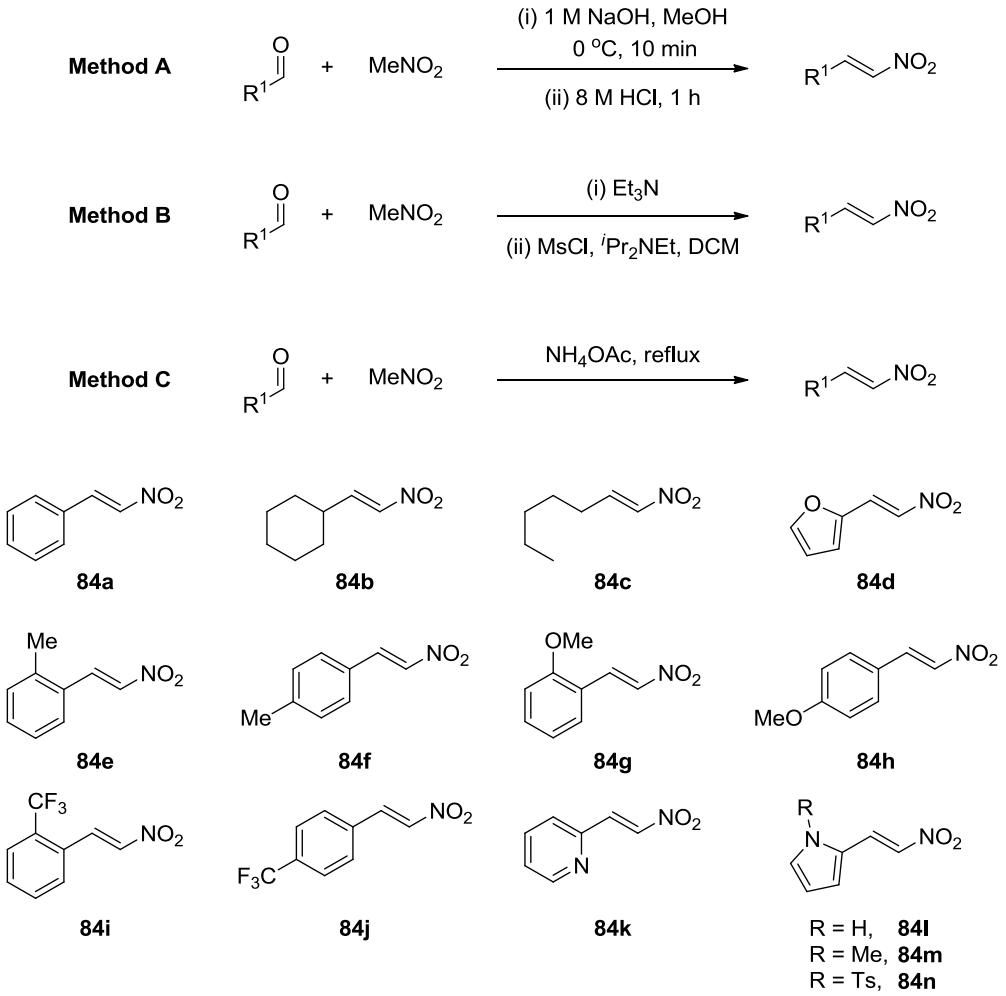
[a] % Conv. to **124a** calculated from ^{1}H NMR. [b] *dr* of crude **124a** calculated from ^{1}H NMR.

Varying the solvent had no significant effect on the reaction. Altering the equivalents of acid had a slightly negative effect on the reaction (Table 1, entries 5-6) and the use of acetic acid did not effectively promote the reaction. It was found that the reaction was complete after stirring for 5 min at room temperature, therefore these conditions were used in further experiments (Table 1, entry 8).

2.1.2 Scope of reductive nitro-Mannich reaction

With the reaction optimised to an acceptable standard the scope of the reaction with respect to the nitroalkene was ready to be tested. A variety of nitroalkenes were then synthesised using three different methods. Nitroalkenes **84a-j** could be synthesised using any of the three methods, and as such the method used was chosen based on their state at room temperature and pressure. Solids were typically formed using method A as the product nitroalkene precipitated upon addition to 8 M HCl, allowing simple isolation of the desired nitroalkene. Whereas, nitroalkenes which existed as

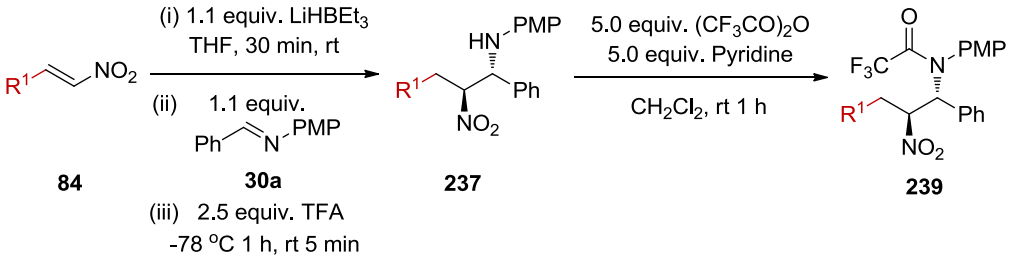
oils were prepared using method B which typically gave greater yields compared to method A.

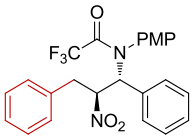
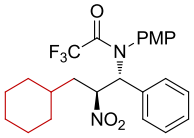
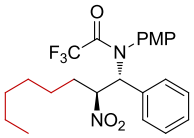
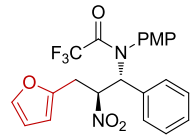
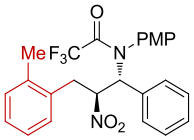
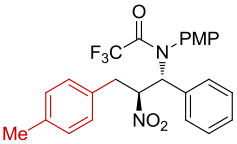
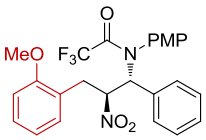
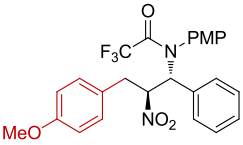
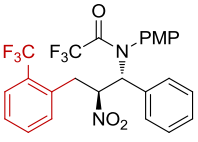


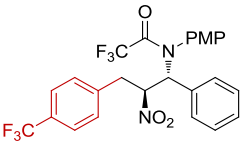
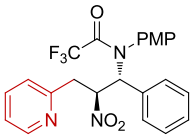
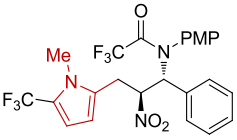
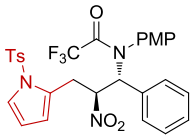
Scheme 90. Synthesis of nitroalkenes

Pyridyl nitroalkene **84k** could only be formed using method B albeit in moderate yield (40%). Pyridyl nitroalkene **84k** had a tendency to degrade at room temperature, presumably due to polymerisation, but could be stored at -20 °C for several weeks and re-purified by rapid column chromatography if required. The unprotected *N*-H Pyrrole nitroalkene **84l** could not be formed under any of the conditions tested and instead formed a black tar, presumably due to polymerisation. As such, *N*-Me pyrrole nitroalkene **84m** was synthesised using method C. Methods A and B produced little to no product for this reaction, the reasons for this failure are unclear but it is plausible that the aldehyde is too electron rich to undergo the initial Henry reaction. *N*-tosylated pyrrole nitroalkene **84n** was synthesised using method B without any difficulties.

Table 2. Reaction scope with respect to nitroalkenes



Entry	R^1	Nitroalkene	% Yield[a]	*dr*[b]	Final product	
1	Phenyl	**84a**	82	>95:5		**239aa**
2	Cyclohexyl	**84b**	82	90:10		**239ba**
3	^{n}Pentyl	**84c**	78	95:5		**239ca**
4	2-Furyl	**84d**	79	>95:5		**239da**
4	2-Tolyl	**84e**	72	95:5		**239ea**
5	4-Tolyl	**84f**	75	>95:5		**239fa**
6	2-MeO-C_6H_4	**84g**	79	95:5		**239ga**
7	4-MeO-C_6H_4	**84h**	86	>95:5		**239ha**
8	2- F_3C-C_6H_4	**84i**	79	>95:5		**239ia**

9	4-F_3C-C_6H_4	**84j**	81	>95:5		**239ja**
10	2-Pyridyl	**84k**	65	>95:5		**239ka**
11	*N*-Me-2-Pyrrole	**84m**	63	>95:5		**240ma**
12	*N*-Ts-2-Pyrrole	**84n**	74	>95:5		**239na**

[a] Isolated yield of **239.** [b] *dr* of **239** calculated from ^{1}H NMR.

With a large number of nitroalkenes now in hand the scope of the reaction was examined (Table 2). The reaction worked well with aliphatic nitroalkenes giving excellent yields and diastereoselectivities (Table 2, entries 2-3). The use of electron rich and electron deficient aromatics had no major effects on the reaction (Table 2, entries 4-9) and the nitro-Mannich reaction also proceeded well using *N*-heterocycles (Table 2, entry 10). When employing *N*-methyl-pyrrole nitroalkene **84m**, although the desired nitro-Mannich product was formed, trifluoroacetylation resulted in an additional electrophilic addition of a trifluoroacetyl group at the 2-position of the pyrrole ring to give **240ma** (Table 2, entry 11). Attempts to prevent this formation by using less equivalents of trifluoroacetic anhydride resulted in a mixture of products.However, using *N*-tosylated pyrrole **84n** allowed the formation of the desired product in good yield without any Friedel-Crafts acylation product forming (Table 2, entry 12). Unlike the unprotected *β*-nitroamines **237**, all of the trifluoroacetylated products **239** were stable for several months at room temperature apart from 2-pyridyl product **239k** which interestingly changed from a yellow to black oil when left to stand for several days. Examination of the ^{1}H NMR showed epimerisation had occurred at the *α*-position to the nitro group, and a new *dr* of 55:45 was observed in favour of the *syn* isomer. No retro-nitro-Mannich products were observed. This is interesting as epimerisation of trifluoracetylated products **239** has not been observed before. Although based on pK_a values pyridine should not readily

deprotonate a nitroalkane (~5 *vs.* ~10), the epimerisation may be facilitated by an intramolecular deprotonation of the *α*-nitro proton by the pyridine nitrogen in the 2-position (Figure 15). Such a deprotonation may be significantly more rapid than an intermolecular deprotonation.

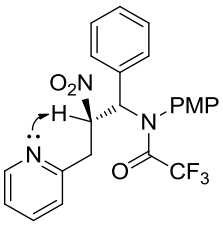
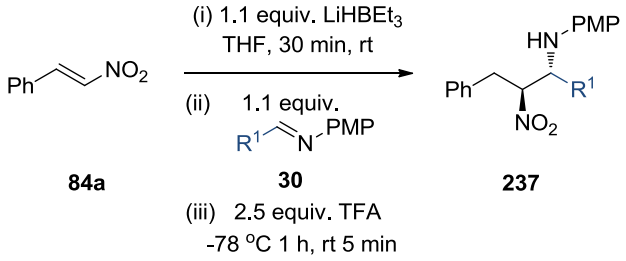


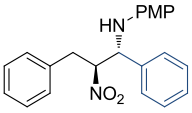
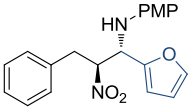
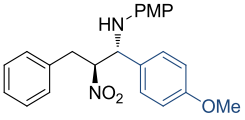
Figure 15. Possible epimerisation mechanism

With the scope of the reaction with respect to nitroalkenes examined, attention was turned towards varying the imine substituents. However, initial investigations with different imines proved problematic (Table 3).

Table 3. Reductive nitro-Mannich reaction with different imines



84a 30 237

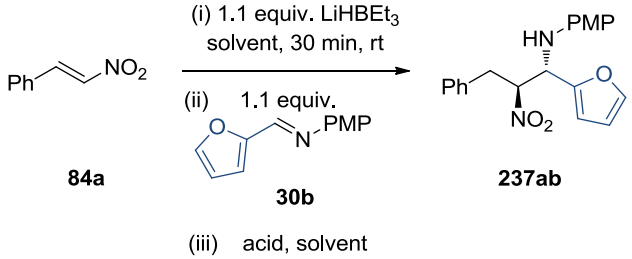
Entry	R^1	Imine	% Conv.[a]	Crude *dr*[b]	Product	
1	Phenyl	**30a**	>95	>95:5		**237aa**
2	2-Furyl	**30b**	>95	65:35		**237ab**
3	4-MeO-C_6H_4	**30e**	>95	85:15		**237ae**

[a] % Conv. to **237** calculated from ^{1}H NMR. [b] *dr* of crude **237** calculated from ^{1}H NMR.

Imines substituted with electron-rich aromatics did not undergo the reaction with the same high levels of diastereoselectivity as the standard phenyl substituted imine **30a**. Imine **30b**, possessing a furyl substituent, was fully converted to desired product

237ab but with low diastereoselectivity (65:35 *dr*, entry 2). The *para*-methoxyphenyl substituted product **237ae** was produced with greater selectivity (85:15 *dr*, entry 3) but this was still lower than previous examples.

Table 4. Optimisation with an electron rich imine



Entry	Acid (N^{o} equiv.)	Solvent	Reaction temp. and time	% Conv.[b]	*dr*[c]
1	TFA (2.5)	THF	-78 ^{o}C 1 h	>95	65:35
2	TFA (2.5)	THF	-100 ^{o}C 1 h	>95	65:35
3	TFA (1.2)	THF	-78 ^{o}C 1 h	>95	75:25
4	AcOH (1.2)	THF	-78 ^{o}C 1 h	<5	n/a
5	AcOH (1.2)	THF	-78 ^{o}C 1 h, rt 1 h	<5	n/a
6	$BrCH_2CO_2H$ (1.2)	THF	-78 ^{o}C 1 h	<5	n/a
7	$BrCH_2CO_2H$ (1.2)	THF	-78 ^{o}C 1 h, rt 1 h	40	65:35
8	Cl_2CHCO_2H (1.2)	THF	-78 ^{o}C 1 h	80	70:30
9	$Cl_3C_2O_2H$ (1.2)	THF	-78 ^{o}C 1 h	>95	80:20
10	TFA[a] (1.2)	THF	-78 ^{o}C 1 h	>95	80:20
11	Me_3SO_3H (1.2)	THF	-78 ^{o}C 1 h	50	80:20
12	TfOH (1.2)	THF	-78 ^{o}C 1 h	>95	80:20
13	TfOH (1.2)	CH_2Cl_2	-78 ^{o}C 1 h	>95	80:20
14	TFA[a] (1.2)	CH_2Cl_2	-78 ^{o}C 1 h	>95	90:10
15	TFA[a] (1.2)	Et_2O	-78 ^{o}C 1 h	>95	65:35
16	TFA[a] (1.2)	Toluene	-78 ^{o}C 1 h	>95	85:15

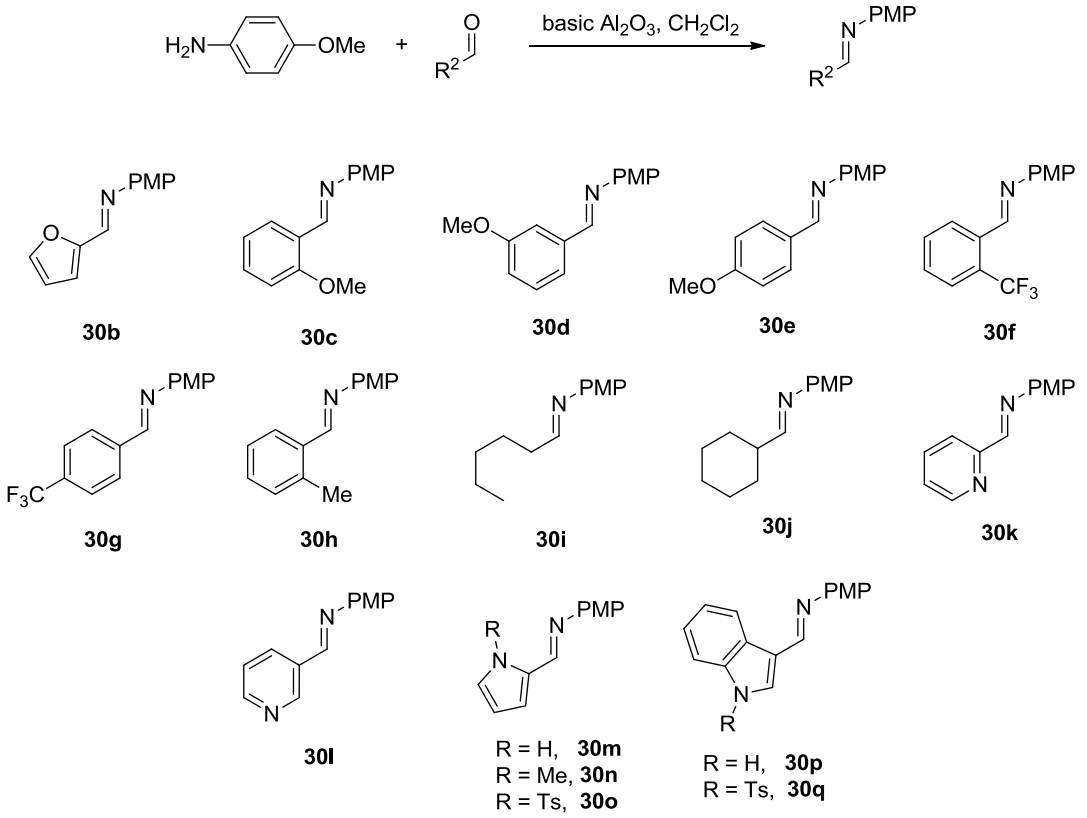
[a] TFA was added to rxn. as a neat solution (normally added in 1 mL solvent). [b] % Conv. to **237** calculated from ^{1}H NMR. [c] *dr* of crude **237** calculated from ^{1}H NMR.

It was hoped that this poor selectivity could be improved upon by further reducing the temperature or by using a weaker acid. A range of different conditions to attempt to optimise the reaction using electron rich imines were then investigated, as shown in table 4. Reducing the temperature to -100 ^{o}C failed to have any effect on the reaction

(Table 4, entry 2). Reducing the equivalents of acid to 1.2 had a slightly positive outcome on the diastereoselectivity of the reaction (1.2 equivalents were used so as to also protonate the excess imine and the remaining Superhydride^{TM} in the reaction) as can be seen in table 4, entry 3. Various acids were tested in the reaction with pK_a values varying from 4.76 to -14. Acetic acid (pK_a = 4.76) and bromoacetic acid (pK_a = 2.86) failed to promote the reaction at –78 ^oC. Acetic acid also failed to promote the reaction after 1 h at room temperature whereas bromoacetic acid caused some reaction at room temperature but could not achieve an improvement in diastereoselectivity. Dichloroacetic acid (pK_a = 1.29), and trichloroacetic acid (pK_a = 0.65) were able to promote the reaction at -78 ^oC and trichloroacetic acid was able to give a slightly improved diastereoselectivity (Table 4, entry 9). This diastereoselectivity could also be achieved using TFA (pK_a = -0.25) as a neat solution (Table 4, entry 10). Presumably this is because a smaller volume of solution is charged to the reaction and this causes less of a temperature increase to the reaction. Charging the acid neat was more difficult with trichloroacetic acid as it is quite a sticky solid at room temperature. Methanesulfonic acid (pK_a = -2.6) also gave a small improvement to the selectivity but was unable to promote the reaction sufficiently to obtain more than a moderate conversion to *β*-nitroamine **237ab**. Triflic acid (pK_a = -14) gave the best diastereoselectivity (Table 4, entry 12) so this acid along with trifluoroacetic acid were used in an additional solvent screen. In dichloromethane the *dr* was greatly improved when using trifluoroacetic acid (Table 4, entry 14) but not when using triflic acid (Table 4, entry 13). The reaction in diethyl ether was poorly diastereoselective (Table 4, entry 15) but in toluene the reaction was also reasonably selective (Table 4, entry 16). The reaction seems to be best in non-coordinating solvents such as dichloromethane and toluene. It is possible that tetrahydrofuran and diethyl ether interfere with the transition state resulting in a less selective reaction.

With new optimised conditions for electron rich imines in hand, the reaction and the scope with respect to a variety of imines could be investigated. A number of imines were synthesised from their corresponding aldehydes using basic alumina as a desiccant (Scheme 91). All of these imines, apart from alkyl chain imines **30i-j**, were crystalline and could be stored at -18 ^oC indefinitely. Cyclohexyl imine **30j** would solidify in the freezer at -18 ^oC and as such could be stored for several months

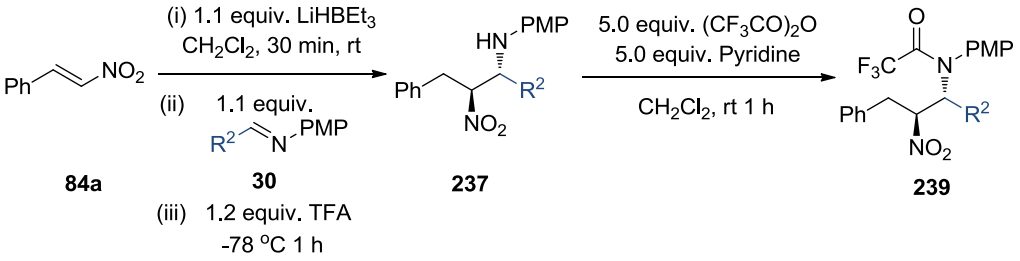
without significant degradation. The ^{n}pentyl imine **30i** rapidly decomposed at room temperature, presumably by enamine formation and subsequent oligomerisation, and consequently was used immediately and had to be prepared at -78 ^{o}C.

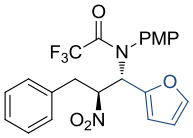
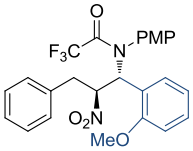
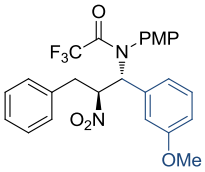
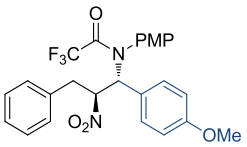
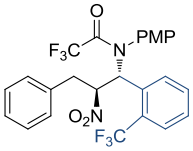
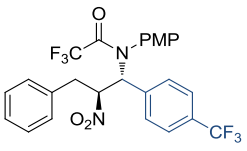
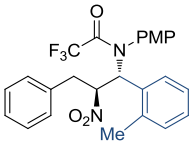


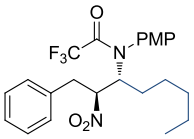
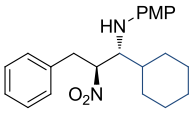
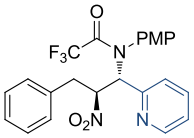
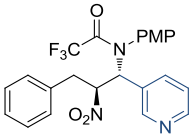
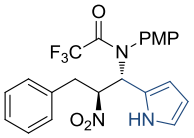
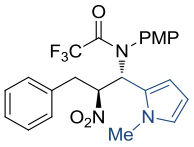
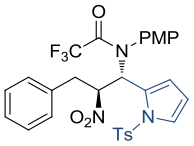
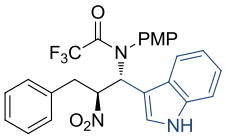
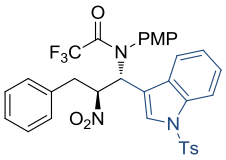
Scheme 91. Synthesis of imines

With a range of imines in hand the scope of the reaction was then examined (Table 5). The reaction worked well for both electron rich and electron deficient aryl imines (Table 5, entries 1, 3, 4 and 6). For more sterically demanding aryl imines with *ortho* substituents (Table 5, entries 2, 5, 7) the diastereoselectivity was slightly reduced but still very respectable, and these diastereomers could often be separated by column chromatography resulting in diastereomerically pure products (Table 5, entry 7). The reaction also worked well with straight chain alkyl imine **30i** (Table 5, entry 8) but was poorly diastereoselective with the bulkier cyclohexyl imine **30j** (Table 5, entry 9). The product from imine **30j** did not undergo trifluoroacetamide protection even with a 5 times excess of trifluoroacetic anhydride and pyridine. Fortunately, it was stable enough to purify by chromatography to give **237aj** as a single diastereomer in a 58% yield. Despite the reactions being performed using dichloromethane as a solvent there was still some tetrahydrofuran present in the reaction as the Superhydride^{TM} is only available as a 1 M solution in tetrahydrofuran.

Table 5. Reaction scope of reductive nitro-Mannich reaction with respect to imine



Entry	R^2	Imine	Yield[a]	*dr*[b]	Final product	
1	2-Furyl	**30b**	83	90:10		**239ab**
2	2-MeO-C_6H_4	**30c**	87	90:10		**239ac**
3	3-MeO-C_6H_4	**30d**	86	>95:5		**239ad**
4	4-MeO-C_6H_4	**30e**	80	>95:5		**239ae**
5	2- F_3C-C_6H_4	**30f**	76	95:5		**239af**
6	4-F_3C-C_6H_4	**30g**	78	>95:5		**239ag**
7	2-Tolyl	**30h**	72	>95:5 (85:15)		**239ah**

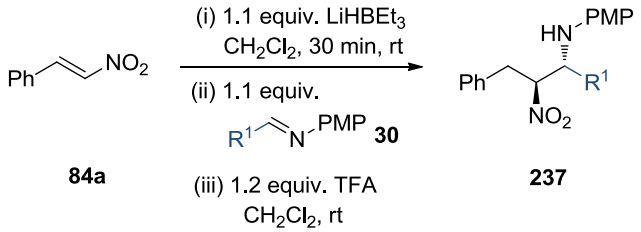
8	^{n}Pentyl	**30i**	84	>95:5		**239ai**
9	Cyclohexyl	**30j**	58	>95:5 (75:25)		**237aj**
10	2-Pyridyl	**30k**	60	>95:5 (75:25)		**239ak**
11	3-Pyridyl	**30l**	80	>95:5		**239al**
12	2-Pyrrole	**30m**	15[c]	50:50[d]		**237am**
13	*N*-Me-2-Pyrrole	**30n**	75[c]	57:43[d]		**237an**
14	*N*-Ts-2-Pyrrole	**30o**	74	>95:5		**239ao**
15	3-Indole	**30p**	80[c]	50:50[d]		**237ap**
16	*N*-Ts-3-Indole	**30q**	64	>95:5 (90:10)		**239aq**

[a] Isolated yield of **239**. [b] *dr* of isolated **239** calculated from ^{1}H NMR, *dr* of crude product given in parentheses if this differed from purified product. [c] % Conv. to **237** calculated from ^{1}H NMR. [d] *dr* of crude **237** calculated from ^{1}H NMR.

It was thought that by removing the tetrahydrofuran *in vacuo* from the reaction after the reduction had been performed, the diastereoselectivity may be further increased. This reaction was performed using nitroalkene **84a** and imine **30j** but unfortunately did not improve the selectivity any further. Nitrogen containing heterocycles were also examined, 2-Pyridyl-*N*-PMP-imine **30k** was subjected to the standard reductive

nitro-Mannich conditions giving a high conversion (>95%) but unfortunately the diastereoselectivity of the reaction was only 75:25 (Table 5, entry 10). However, 3-pyridyl analogue **30l** worked very well giving essentially a single diastereomer in 80% yield (Table 5, entry 11). Pyrrole containing imines **30m** and **30n** were poorly selective and *N*-*H*-pyrrole imine **30m** also gave a low conversion (Table 5, entries 12-13). This is presumably due to the electron rich nature of these imines. Protecting the pyrrole with an electron withdrawing group, such as a tosyl group, resulted in a much more reactive and stereoselective nitro-Mannich reaction (Table 5, entry 14). A similar reactivity pattern was observed with the indole imines **30p** and **30q**, again a tosyl group was required to obtain good diastereoselectivity (Table 5, entries 15-16).

Table 6. Reductive nitro-Mannich reaction at room temperature



Entry	R^1	Imine	Rxn. time	% Conv.[b]	*dr*[c]
1	Phenyl	**30a**	5 min	>95	90:10
2	Phenyl	**30a**	3.5 h	>95	85:15
3[a]	Phenyl	**30a**	5 min	66	85:15
4	2-Furyl	**30b**	5 min	>95	85:15
5	2-Tolyl	**30h**	5 min	>95	80:20

[a] Reaction performed in THF. [b] % Conv. to **237** by ^{1}H NMR. [c] *dr* of crude **237** calculated from ^{1}H NMR.

As the change of solvent from tetrahydrofuran to dichloromethane had shown such a good improvement in selectivity, the reaction was attempted at room temperature to see if any preferential selectivity would still exist. Remarkably even at room temperature the reaction in dichloromethane showed good diastereoselectivity, albeit not as impressive as when the reaction was performed at low temperature (Table 6, entry 1). Additionally, when left to stir at room temperature for long periods of time, the diastereoselectivity of the reaction also remained high (Table 6, entry 2). In tetrahydrofuran however, the reaction is not as efficient or selective (Table 6, entry 3), even when stirred for longer periods of time the conversion to the desired product

did not improve. Presumably in tetrahydrofuran at room temperature the rate of quenching of the nitronate is more competitive with the nitro-Mannich reaction than in dichloromethane, although the reasons for this are unclear. The reaction also showed good diastereoselectivity with electron rich 2-furyl imine **30b** (Table 6, entry 4), greater even than the selectivity obtained using tetrahydrofuran at -78 ^{o}C (Table 4, entry 3). Using more sterically demanding imines with *ortho* substituents slightly reduced the diastereoselectivity (Table 4, entry 5).

2.1.3 Assignment and origin of relative stereochemistry

So far all of the examples of the nitro-Mannich reaction in this research have depicted the major diastereomer as the *anti*-product. These assignments are based on the ^{1}H NMR coupling constants of the unprotected *β*-nitroamine products **237**. This method of assignment was based on the prior work by Seebach *et al*. from their seminal work on the Henry reaction.[126] There, the authors proposed that the *β*-nitroalcohol products would preferentially exist in a H-bonded *pseudo* chair conformation. In such a conformation, the coupling constants could be compared to those observed in cyclohexane structures to identify axial-axial or axial-equatorial couplings. It was assumed that *β*-nitroamines **237** would adopt a similar conformation and the same strategy could be applied to assign the diastereomers with the axial-axial coupling larger than the axial-equatorial coupling (Figure 16, full tables of coupling constants can be found in appendix 5.2). This method of analysis has since been supported by the solving of the crystal structures of several trifluoroacetamides using single crystal X-ray crystallography.[118,127]

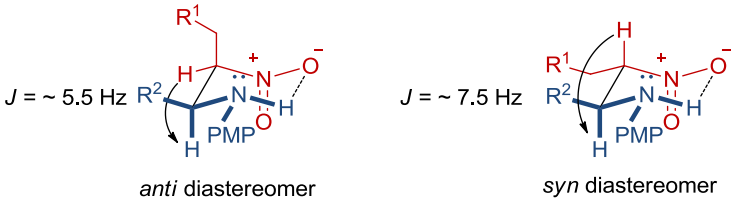


Figure 16. Assignment of relative stereochemistry

Although this method of assignment provided coupling constants within similar ranges for the majority of examples, further suggesting its suitability for determining the relative stereochemistry, there were some cases where the coupling constants were not conclusive. This was common with *β*-nitroamines derived from more hindered *ortho*-substituted imines **30c**, **30f** and **30h**; as well as cyclohexyl imine **30j**

and 2-pyridyl imine **30k**. In the case of cyclohexyl imine derived *β*-nitroamine **237aj**, a larger coupling constant (7.8 Hz) was observed for the major diastereomer, suggesting the *syn* diastereomer. Whereas the minor diastereomer had a smaller coupling constant (4.8 Hz), suggesting formation of the *anti* diastereomer. In similar work within the Anderson group, another analogue closely resembling **237aj** also possessed coupling constants differing from those expected for the protons in the *α*-positions of the amino and nitro functionalities. The crystal structure of this analogue has since been solved, thus confirming the preference for the *anti* diastereomer (Figure 17). So for this reason, we tentatively assign *β*-nitroamine **237aj** as the *anti* diastereomer.

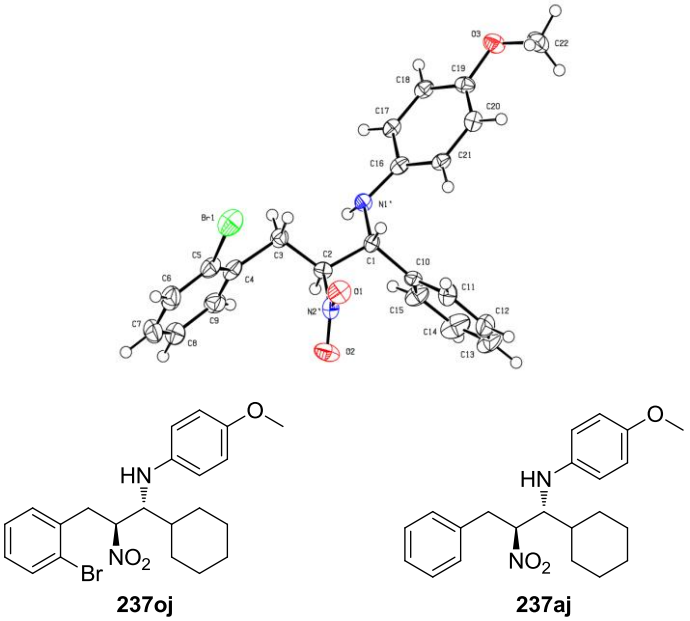


Figure 17. Single X-ray crystal structure of similar analogue

With regards to the other *β*-nitroamines with inconclusive coupling constants, it is thought that the *ortho*-substituents may interfere with a cyclic conformation resulting in less characteristic *J*-values. The 2-pyridyl substituted *β*-nitroamine **237ak** may be doing something similar as interestingly 3-pyridyl substituted *β*-nitroamine **237an** has coupling constants within the expected ranges. For these reasons, *β*-nitroamines **237ca**, **237fa**, **237ha**, and **237ak** are somewhat tentatively assigned as *anti* diastereomers.

Previous reports have observed that the *syn* diastereomer is the thermodynamic product. This is also suggested when examining the cyclic intramolecular H-bonded structures shown in figure 16 as this diastereomer places all of the larger substituents

into the *pseudo* equatorial positions. Therefore it suggests that the nitro-Mannich reaction is under kinetic control and that the *anti* diastereomer should be formed by the lowest energy transition state. It is proposed that the preference for the *anti* diastereomer originates from a cyclic transition state as depicted in figure 18. As the imine is locked in an *E* configuration, both the PMP group and the R^2 substituent are forced into *pseudo* axial positions in order for a successful H-bonding network to form.

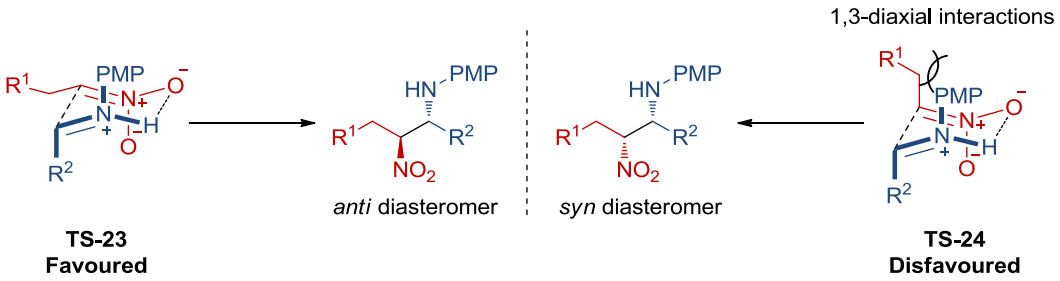


Figure 18. Proposed origin of diastereoselectivity

The substituent on the nitro-partner can then either adopt a *pseudo* equatorial (**TS-23**) or a *pseudo* axial (**TS-24**) position. The most favoured position to adopt is the *pseudo* equatorial position as this would avoid any unfavourable 1,3-diaxial interactions. Because of this desire to minimise diaxial strain we believe the *anti* diastereomer is formed preferentially.

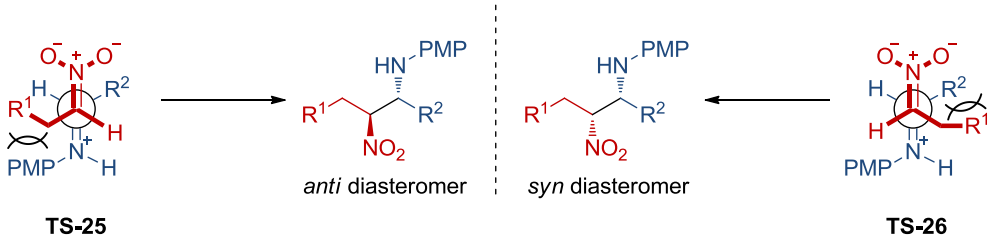


Figure 19. Acyclic transition states for the nitro-Mannich reaction

An alternative reaction pathway could proceed *via* an acyclic transition state (Figure 19). However, both of the possible acyclic transition states suffer from steric clashes and it seems unlikely that the reaction proceeds *via* such a transition state due to the high level of diastereoselectivity observed. These proposed transition states may also offer some insight into the cause of some interesting and anomalous results obtained during the course of this research. Firstly, the higher diastereoselectivities obtained when using non-coordinating solvents such as dichloromethane and toluene instead of tetrahydrofuran and diethyl ether. It is proposed that ethereal solvents such as

tetrahydrofuran and diethyl ether may interfere with the hydrogen bonding make-up of the transition state. Several solvent molecules could break up the intramolecular H-bonding structure and hence favour an acyclic pathway which may be less selective (Figure 20).

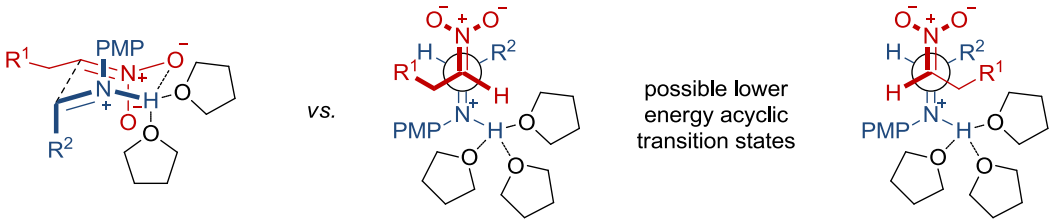


Figure 20. Possible effect of coordinating solvents on nitro-Mannich reaction

A second example can be found in the poor diastereoselectivity of the reaction when using cyclohexyl imine **30j** when only a 75:25 ratio was observed. It was earlier suggested that the coupling constants observed for *β*-nitroamine **237aj** were not indicative of a cyclic conformation. This could mean that the cyclic transition state is also not of a low energy and as such the reaction proceeds *via* an acyclic pathway. As to reasons for such a difference in energy, as yet we are unable to suggest why the cyclohexyl group would not favour a cyclic structure.

2.1.4 Concluding paragraph

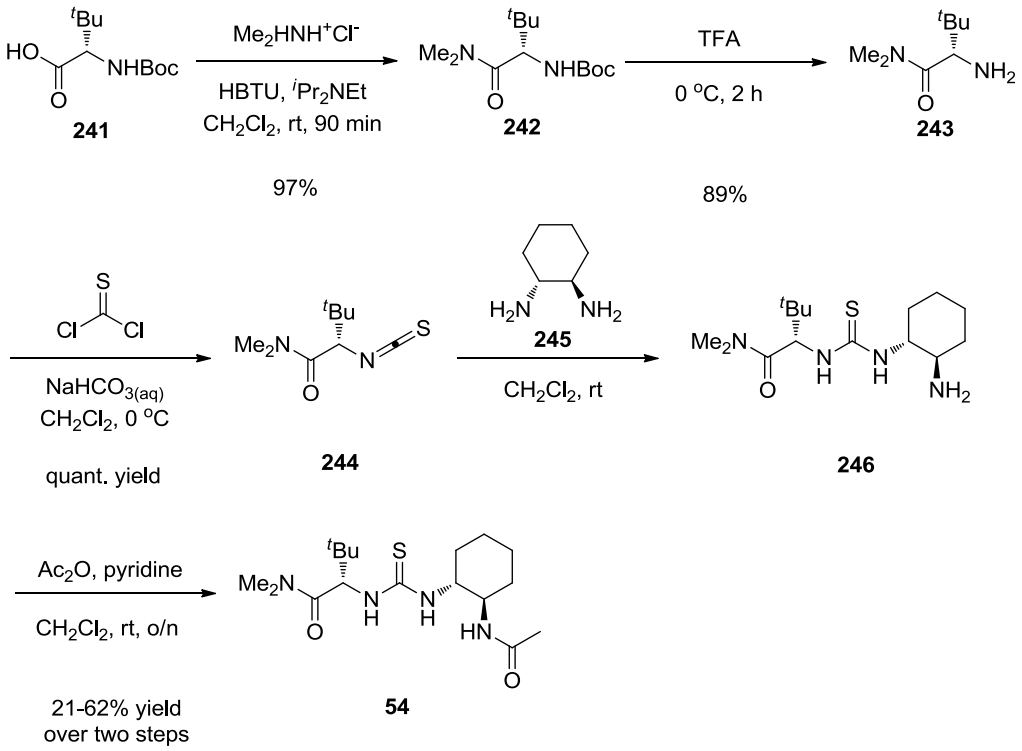
In this first section, the development of a racemic reductive nitro-Mannich reaction has been described. Continuing from preliminary studies performed in the Anderson group, this research has overcome the initial limitation of the reductive nitro-Mannich reaction where *β*-nitrostyrenes were not tolerated. This was achieved by using *N*-PMP protected imines **30a** in place of *N*-OMB protected imines **230**; and the use of a stronger Brønsted acid, namely trifluoroacetic acid in place of acetic acid. The reaction worked well with a variety of nitroalkenes however upon examining a range of electron rich imines in the reaction the diastereoselectivity was significantly reduced. It was discovered that by using non-coordinating solvents such as dichloromethane the diastereoselectivity could be greatly increased and a variety of different imines could be employed in the reaction to give the desired *β*-nitroamines **237** in high conversion and excellent diastereoselectivity. The *β*-nitroamine products **237** were unstable to standard purification techniques and as such were protected as trifluoroacetamides **239** to enable their isolation in good yields (58-87% yield) and

diastereoselectivity (up to >95:5 *dr*) enriched in the *anti*-form. The high levels of diastereoselectivity are thought to originate from a cyclic transition state.

2.2 Tandem asymmetric reductive nitro-Mannich reaction

2.2.1 Initial investigations

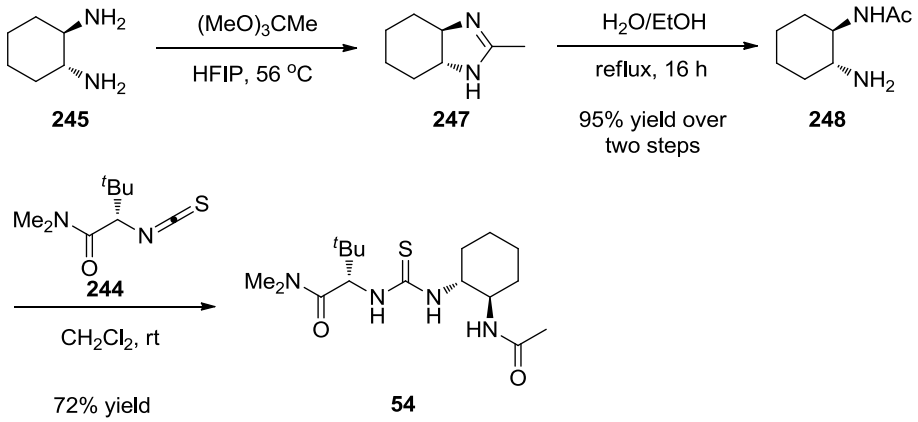
After successfully developing a racemic reductive nitro-Mannich reaction, attention was turned towards an enantioselective variant. As described in section 1.4, it was proposed that thiourea organocatalysis may offer an effective method to achieve such an aim. Initially it was decided to synthesise thiourea organocatalysts **54** and **191** which have been successfully used by the groups of Jacobsen,[33] and List,[102] in nitro-Mannich reactions and reductions of nitroalkenes respectively. Jacobsen's catalyst was initially synthesised as described in the original publication (Scheme 92). However, in our hands the final two steps proved problematic and suffered from irreproducible yields.



Scheme 92. Literature synthesis of Jacobsen's thiourea organocatalyst[33]

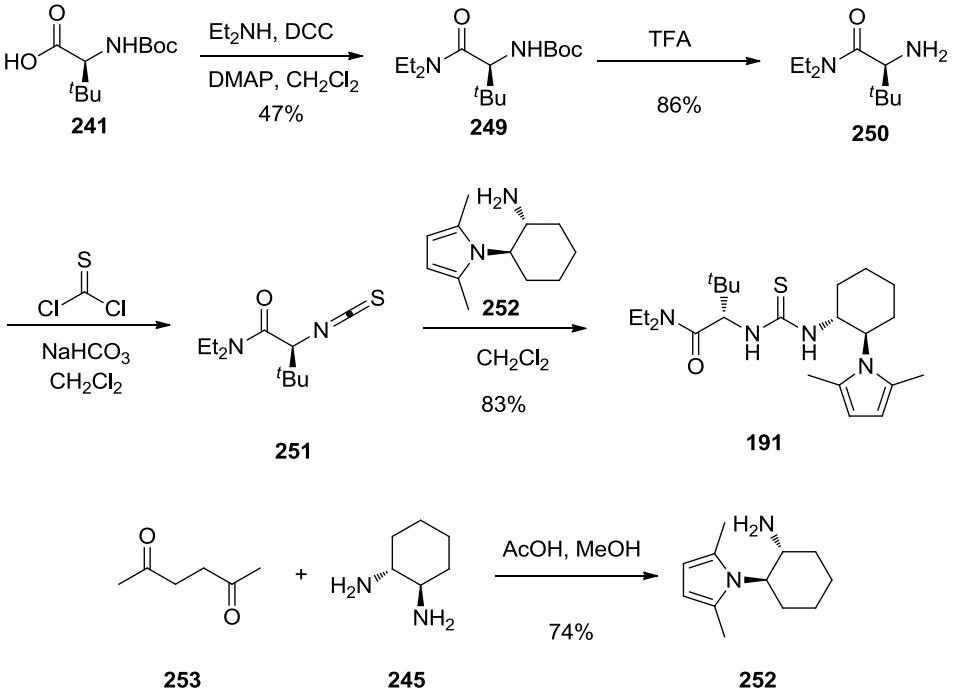
This was presumably due to the poor selectivity for the reaction of diamine **245** with isothiocyanate **244**, which could form a bis-urea compound; as well as difficulty in purifying resultant amine **246** which gave variable yields after chromatography.

Performing these last two reactions in one-pot rather than purifying **246** also had no positive effect on the reproducibility of the reaction. To circumvent these problems it was attempted to mono-acetylate diaminocyclohexane **245**. This was successfully performed by first synthesising benzoimidazole **247**, which has been previously synthesised using an *in situ* formed Pinner salt of acetonitrile under dry conditions,[128] or more conveniently by simply refluxing trimethyl orthoacetate in hexafluoroisopropanol (HFIP).[129] Benzoimidazole **247** can then be simply hydrolysed to give the desired mono-acetylated diamine **248** (Scheme 93). By then reacting mono-acetylated diamine **248** with isothiocyanate **244** an excellent and reproducible yield of 72% could be achieved.



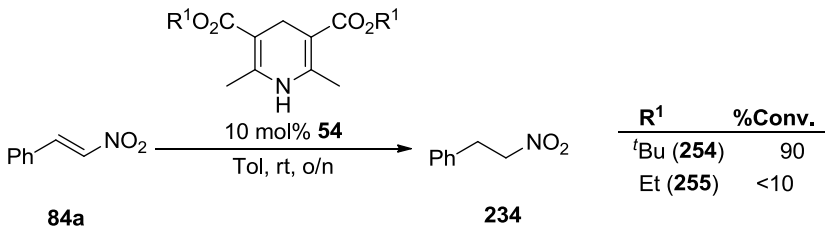
Scheme 93. Alternative synthesis of Jacobsen's thiourea organocatalyst

The synthesis of List's thiourea catalyst **191** proved less problematic with the only low yielding step being the coupling of diethylamine with the Boc-protected amino acid **241** forming amide **249** in 47% yield (Scheme 94). Boc-deprotection proceeded in good yield in neat TFA to give amine **250** which was then reacted with thiophosgene to give isothiocyanate **251**. Isothiocyanate **251** was then used without further purification to give final thiourea **191** by stirring with chiral diamine **252** in an overall yield of 34% for the 4 linear steps. Diamine **252** could itself be formed simply by the condensation of diaminocyclohexane **245** with diketone **253**.



Scheme 94. Synthesis of List's thiourea catalyst

With these two catalysts synthesised, attention was turned towards the reductive nitro-Mannich reaction. Whereas List's thiourea **191** has been previously shown to catalyse the reduction of nitroalkenes by Hantzsch esters, Jacobsen's catalyst **54** had not previously been examined in such a reaction. It seemed prudent to examine its potential before commencing more complicated two-step reactions. The reduction of *β*-nitrostyrene **84a** using Jacobsen's catalyst **54** was investigated using Hantzsch esters **254** and **255**. Pleasingly, 70% reduction after 3 h occurred using *tert*-butyl Hantzsch ester **254**, increasing to 90% conversion after 16 h. Interestingly, less than 10% conversion was observed when using **255** as the hydride source (Scheme 95). This large discrepancy is difficult to explain at first glance as there is minimal difference in electronics between the two species and the *tert*-butyl group seems too far away to be inducing a steric effect.



Scheme 95. Reduction of *β*-nitrostyrene using Jacobsen's catalyst

Intrigued by this difference in reactivity, a thorough search of the literature was performed to discover if this is a general trend or a rare phenomenon. Surprisingly, only one other report, from the Macmillan group, described such a difference in the reactivity of these two hydride sources.[130] Eventually the authors were able to shed some light upon the cause of the difference in reactivity when the crystal structures of the two Hantzsch esters were solved by X-ray crystallography.[131] It was revealed that **254** exists in a puckered conformation which results in two different C-H bond lengths and one C-H bond sitting in the same plane as the π-orbitals, presumably due to the steric effect of the ^{t}Bu groups. In this conformation, the π-orbitals can donate into the C-H σ*-orbital weakening it and greatly increasing its reactivity towards electrophiles. Conversely, Hantzsch ester **255** was planar and the two C-H bonds were of equal length (Figure 21).

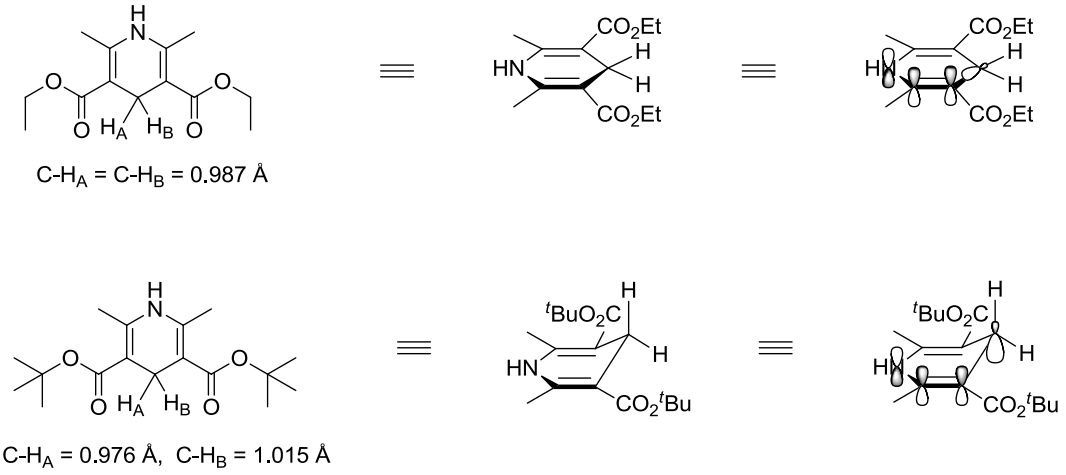
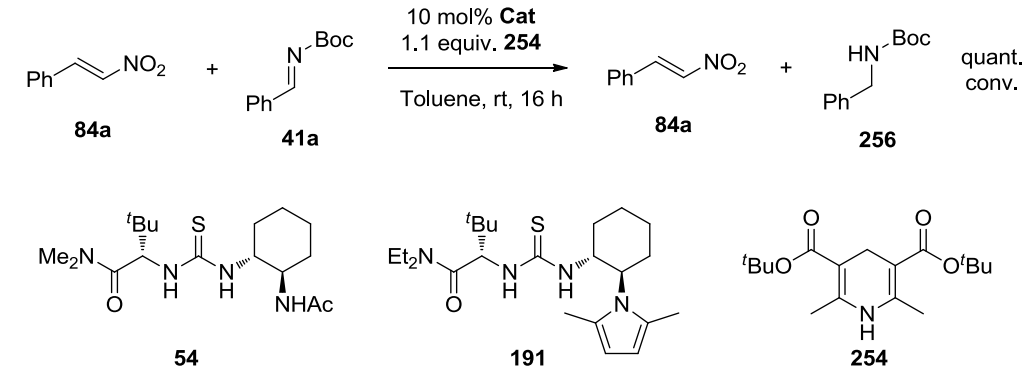


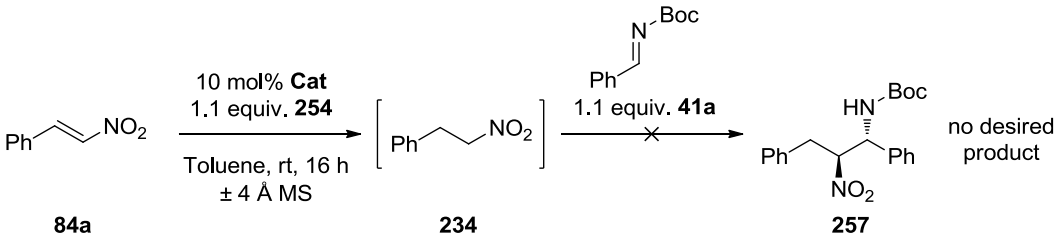
Figure 21. Crystal structures of Hantzsch esters

With this knowledge in hand, the reductive nitro-Mannich reaction was attempted using the *tert*-butyl Hantzsch ester **254**. Due to its use in most thiourea-catalysed nitro-Mannich reactions, *N*-Boc imine **41a** was utilised as the imine electrophile. Initial attempts to perform the reaction in tandem were thwarted as perhaps unsurprisingly, the *N*-Boc imine was reduced in preference over *β*-nitrostyrene **84a** when using either catalyst (Scheme 96).



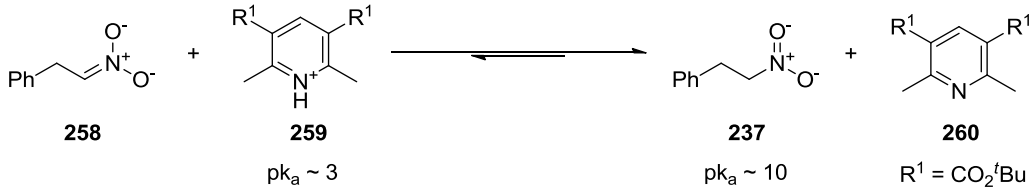
Scheme 96. Attempted tandem reductive nitro-Mannich reaction with *N*-Boc imine **41a**

Subsequently, a two-step, one-pot reaction was attempted. The reduction was left overnight to ensure complete conversion before *N*-Boc imine **41a** was added. No desired product was observed; instead the imine was hydrolysed. This is a common occurrence with *N*-Boc imines so 4 Å powdered molecular sieves were added to the reaction to prevent this degradation. Again no nitro-Mannich product was observed upon addition of the *N*-Boc imine **41a**.



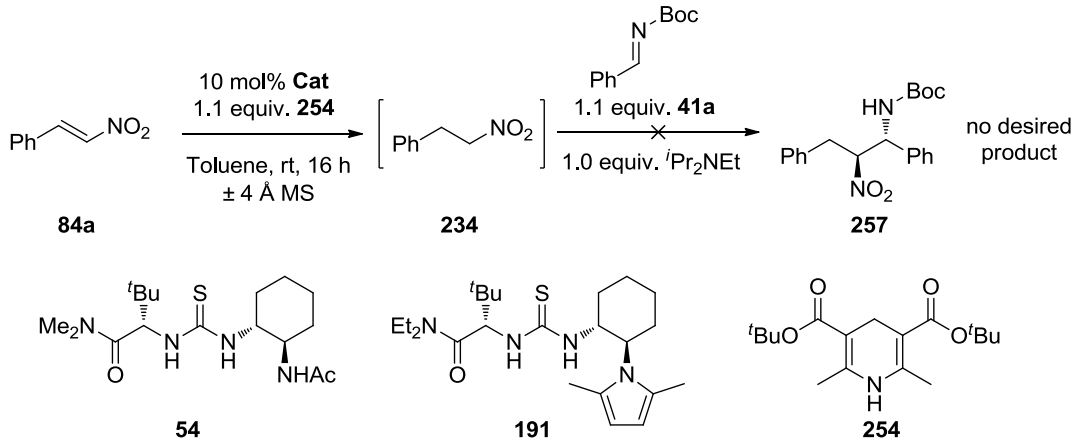
Scheme 97. Two-step one-pot reaction with *N*-Boc imines

This was not unexpected as nitroalkane **234** needs to be deprotonated for the nitro-Mannich reaction to occur. Although nitronate **258** should be initially formed from the reduction of *β*-nitrostyrene, due to the large difference in acidity it would be protonated by pyridinium species **259**. This equilibrium is likely to favour nitroalkane **234** and pyridine **260** and hence no nitro-Mannich reaction occurs (Scheme 98).



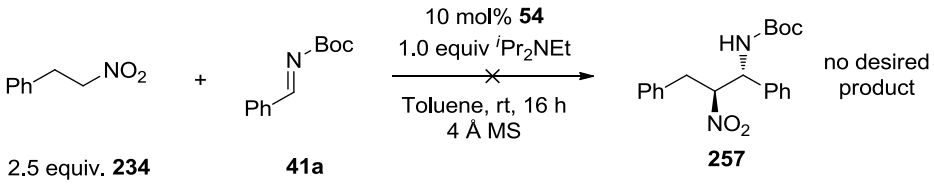
Scheme 98. Equilibrium between nitroalkane and nitronate

To overcome this, an equivalent of Hunig's base ($^{i}Pr_2NEt$) was added to the reaction after complete reduction. Once more no desired reaction was observed with either catalyst (Scheme 99).



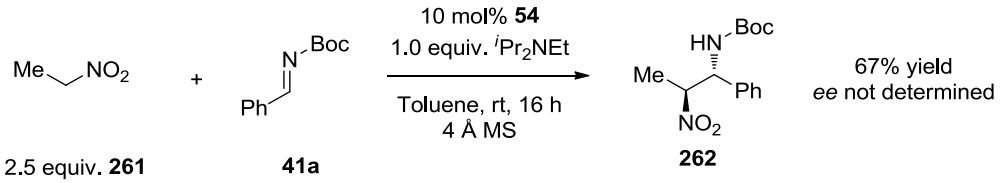
Scheme 99. Two-step one-pot reaction with added base

This lack of reactivity was confusing as these conditions were close to mimicking those used by Jacobsen's group in their nitro-Mannich reactions with catalyst **54**.[33] Essentially the only differences between these reactions that could prevent formation of desired product **257** was the presence of pyridine **260**.



Scheme 100. Attempted nitro-Mannich reaction of nitroalkane **234**

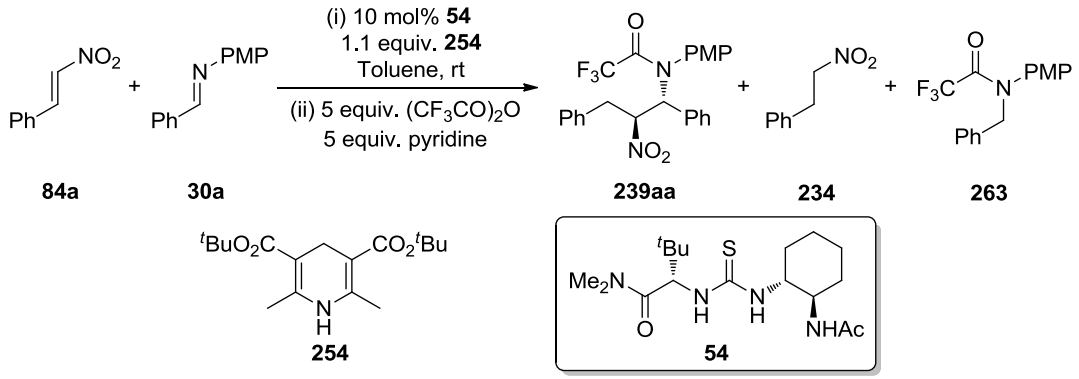
To check that it indeed was pyridine **260** that was hindering the reaction, a simple nitro-Mannich reaction using Jacobsen's exact conditions was performed. Interestingly no reaction was observed even after several days at room temperature (Scheme 100). This result brought into question the purity of our reagents and so one of the reactions from Jacobsen's original publication using nitroethane **261** was repeated so that the suitability of our materials could be evaluated. Pleasingly, the reaction proceeded in a similar fashion to how it was reported in the literature, although the enantioselectivity was not determined (Scheme 101). Satisfied that the starting materials were of adequate purity, it was thought that simply nitroalkane **234** and *N*-Boc imine **41a** do not undergo a nitro-Mannich reaction with Jacobsen's catalyst; however the reasons for this are unknown.



Scheme 101. Repeat of literature reaction using Jacobsen's catalyst

After these results, attention was focused on *N*-PMP imine **30** with which excellent results for the racemic reaction had already been achieved. As such, a tandem reaction with equimolar amounts of *β*-nitrostyrene **84a**, *N*-PMP imine **30a**, Hantzsch ester **254** and 10 mol% Jacobsen's catalyst **54** was investigated (Table 7).

Table 7. Initial investigations into asymmetric reaction with *N*-PMP imine **30a**

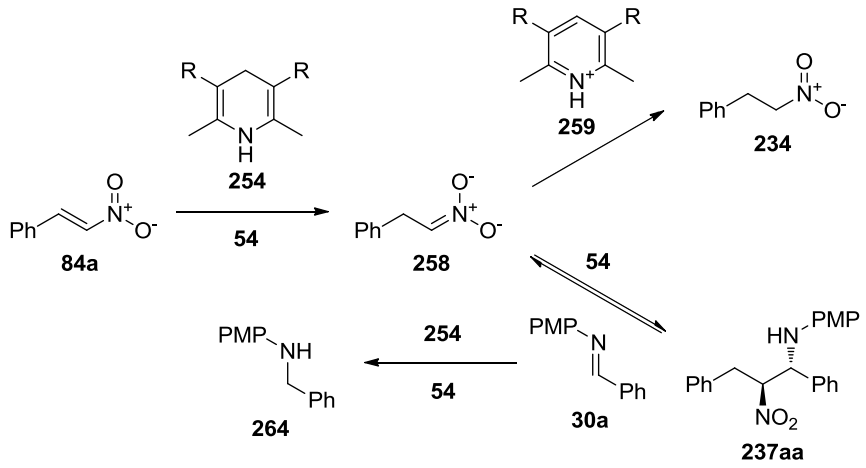


Entry	Rxn. time	% Conv.[a] to 239aa	% Conv.[a] to 234	% Conv.[a] to 263	Yield[b] of 239aa	*dr*[a] of 239aa	% *ee*[c] of 239aa
1	2 h	60	10	5	29	95:5	58
2	9 h	70	30	5	45	95:5	52
3	22 h	60	40	10	23	95:5	44
4[d]	2 h	45	10	10	26	95:5	56
5[e]	2 h	75	15	<5	60	95:5	54
6[f]	2 h	90	35	5	77	95:5	50

[a] Calculated from ^{1}H NMR before trifluoroacetamide protection, based on limiting reagent. [b] Isolated yield of **239aa**. [c] Determined by chiral HPLC. [d] Reaction performed with 2.0 equiv. **30a**. [e] Reaction performed with 2.0 equiv. **84a**. [f] Reaction performed with 2.0 equiv. **84a** and 2.0 equiv. **254**.

Gratifyingly, a positive result was obtained immediately and desired nitro-Mannich product **239aa** was isolated in a 29% yield, with a *dr* of 95:5 and a respectable 58% *ee* after 2 h at room temperature (Table 7, entry 1). Extended reaction times initially led to increased yields up until 9 h, at which point complete consumption of

β-nitrostyrene **84a** was observed, and the product was isolated in a 45% yield and a slightly reduced 52% *ee* (Table 7, entry 2). After that point, the reaction yield decreased (23% after 22 h) and the enantioselectivity was reduced further to 44% *ee* (Table 7, entry 3). Before initiating a catalyst screen, a quick optimisation of the reagent stoichiometry was performed in an attempt to improve the reaction yields. It was observed that increasing the equivalents of *N*-PMP imine **30a** had no noticeable effect on the reaction (Table 7, entry 4). However increasing the equivalents of *β*-nitrostyrene **84a** did have a positive effect and the isolated yield was increased to 60% after 2 h (Table 7, entry 5). Increasing the equivalents of Hantzsch ester **254** further increased the isolated yield to give 87% **239aa** albeit in a slightly reduced 50% *ee* (Table 7, entry 6). In addition to the desired product, a small amount of reduced imine was observed in each case (5-20%) and this was also decreased when using an excess of nitroalkene.



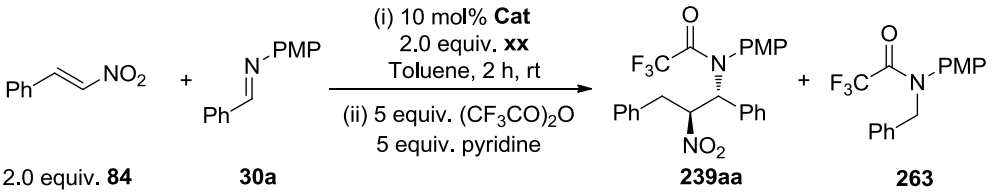
Scheme 102. Possible permutations of one-pot reaction with *N*-PMP imines

As can be seen from scheme 102, the reaction is more complicated than it may first appear. After initial reduction of *β*-nitrostyrene **84a**, nitronate anion **258** can either undergo a catalyst controlled nitro-Mannich reaction with imine **30a** or simply be protonated by pyridinium **259** to give nitroalkane **234**. Of these two processes, the nitro-Mannich reaction is reversible whereas the protonation is irreversible and hence as the reaction progresses the product can be funnelled to nitroalkane **234** reducing the reaction yield. In addition to this, reduction of imine **30a** to give amine **264** adds another complication to the reaction. However, despite these problems it was felt that the reaction conditions were promising enough to conduct a large catalyst screen for the reaction.

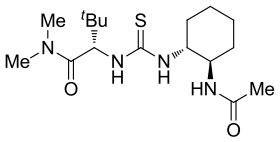
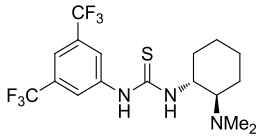
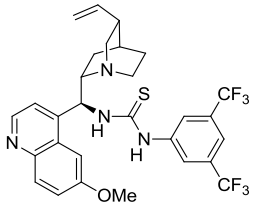
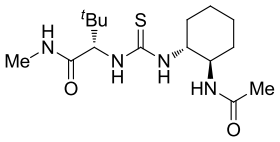
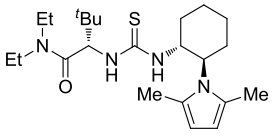
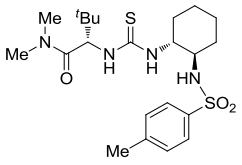
2.2.2 Catalyst screen for the tandem reductive nitro-Mannich reaction

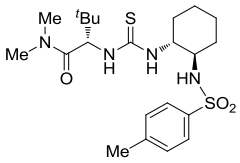
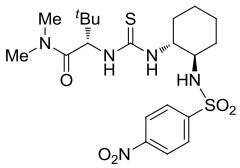
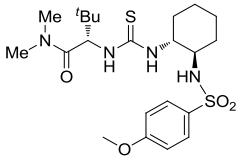
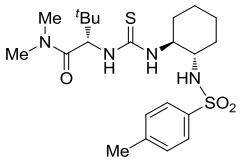
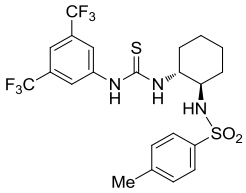
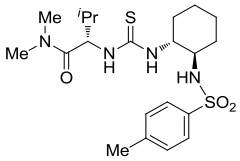
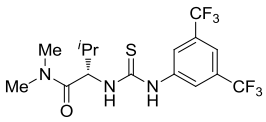
Using the optimised reaction conditions (Table 7, entry 6) a variety of catalysts were examined in the reductive nitro-Mannich reaction (Table 8). Firstly, two commercially available thioureas **49** and **160** were examined in the reaction but no reaction was observed with either (Table 8, entries 2-3). In fact, less than 5% reduction of *β*-nitrostyrene **84a** was detected. It may be that the basic functionality present in these catalysts is preventing reduction from occurring as List's group also saw no reduction of nitroalkenes when similar thioureas were examined.[102] Subsequently, catalyst **265** bearing an extra H-bond donor on the amide was examined as it was felt that this may help stabilise the transition state of the reaction. This theory proved false as the enantioselectivity of the reaction with this catalyst was poor giving **239aa** in only 12% *ee* with a 60% conversion (Table 8, entry 4). List's thiourea catalyst **191** was also examined and pleasingly delivered **239aa** in an excellent 86% *ee* albeit with a greatly reduced reaction yield of 25% (Table 8, entry 5). Interestingly, near complete reduction of *β*-nitrostyrene **84a** had occurred so it appears that this catalyst does not promote the nitro-Mannich reaction as well as **54**. This result, prompted alteration of the group attached to the diaminocyclohexane moiety. Due to the ease of formation of mono-tosylated diaminocyclohexanes,[132] catalyst **266** could be quickly synthesised in an analogous route to Jacobsen's catalyst (Scheme 93) and was as such investigated in the reductive nitro-Mannich reaction (Table 8, entry 6). Pleasingly, thiourea **266** supplied desired product **239aa** in a moderate 48% yield but more importantly with an excellent level of stereocontrol (>95:5 *dr*, 90% *ee*). The moderate yield was simply due a slower relative rate of reaction than when using catalyst **54** and hence the yield could be increased by prolonging the reaction time to 5 h to give **239aa** in a 72% yield with a *dr* of >95:5 and in a slightly reduced 88% *ee* (Table 8, entry 7). Afterwards, the electronics of the sulfonamide were altered to measure the effect on the reaction. As such catalysts **267** and **268** were synthesised and examined in the reaction (Table 8, entries 8-9). Essentially no difference in enantioselectivity was observed with these catalysts but significant differences could be observed in the relative rates of reaction and the more electron withdrawn sulfonyl group provided the fastest rate of reaction.

Table 8. Catalyst screen for asymmetric tandem reductive nitro-Mannich reaction



2.0 equiv. **84** **30a** **239aa** **263**

Entry	Catalyst		%Conv.[a] to 239	%Conv.[a] to 263	Yield[b] of 239	*dr*[a] of 239	% *ee*[c] of 239
1		**54**	90	5	77	95:5	50
2		**49**	<5	<5	n.d.	n.d.	n.d.
3		**160**	<5	<5	n.d.	n.d.	n.d.
4		**265**	60	15	47	95:5	12
5		**191**	30	5	25	>95:5	86
6		**266**	55	10	48	>95:5	90

7[d]		**266**	80	10	72	>95:5	88
8		**267**	80	10	67	>95:5	89
9		**268**	55	15	45	>95:5	90
10		**269**	50	25	37	>95:5	76
11		**270**	60	40	36	95:5	-64
12		**271**	90	5	72	>95:5	90
13		**272**	90	5	75	90:10	90

[a] Calculated from ^{1}H NMR before trifluoroacetamide protection, based on limiting reagent. [b] Isolated yield of **239aa**. [c] Determined by chiral HPLC. [d] Reaction time of 5 h.

Conscious of the possibility that only one side of the catalyst may be influencing the enantioselectivity of the reaction, catalyst **270**, which does not contain the amino acid

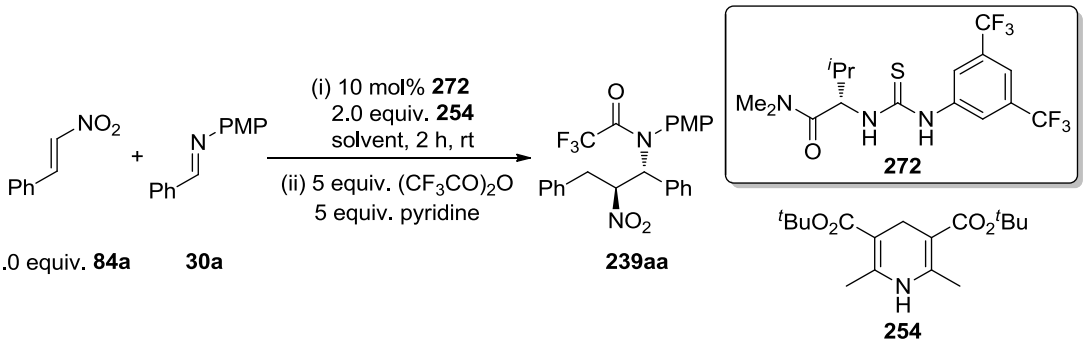
derived side-chain; and mismatched catalyst **269** were synthesised. Mismatched catalyst **269** formed the same enantiomer as **266** but in lower yield and enantiopurity (37% yield, 76% *ee*). The reaction was also much less selective, forming significantly more reduced imine **263** than previous reactions (Table 8, entry 10). Curiously, catalyst **270** formed the opposite enantiomer (-64% *ee*) and also produced a lot more reduced imine **263** than other reactions (Table 8, entry 11). These two results suggested that the diaminocyclohexane moiety was not responsible for the high levels of enantioselectivity. In addition to finding the part of the catalyst responsible for the high stereoselectivity, producing a cheaper catalyst seemed a valuable aim. Mindful of the high price of un-natural amino acid *L*-*tert*-leucine, which was the starting material in our catalyst synthesis, the use of natural amino acid *L*-valine was investigated and catalyst **271** was synthesised. Pleasingly, no noticeable difference in stereoselectivity was observed when using this catalyst and additionally the relative rate of reaction (based on the rate of formation of desired product **239aa** after 2 h) was significantly enhanced compared to catalyst **266**, yielding 72% of **239aa** with a *dr* of >95:5 and in 90% *ee* (Table 8, entry 12). Combining the concepts of these last few experiments, simple catalyst **272** was prepared and remarkably desired product **239aa** was formed in a 75% yield and in 90% *ee* with only a slight reduction in the *dr* of 90:10 (Table 8, entry 13). It was thought that the small drop in the diastereoselectivity was more than compensated for by the simplicity of catalyst **272** and could be easily overcome with some further optimisation. Hence, catalyst **272** was the chosen catalyst from the screen.

2.2.3 Optimisation of reaction with selected catalyst

With catalyst **272** chosen, further optimisation of the reaction to improve the diastereoselectivity was carried out. Initially, solvents were examined to confirm that toluene was the ideal choice (Table 9). Dichloromethane gave essentially identical results to toluene although slightly more reduced imine **263** was observed (Table 9, entry 2). Diethyl ether also gave a good yield but the enantioselectivity of the reaction was greatly reduced to 16% *ee* (Table 9, entry 3). Interestingly, the reaction in tetrahydrofuran was very selective (94% *ee*) but the reaction yield after 2 hours was only 13% suggesting a significantly slower rate of reaction (Table 9, entry 4). Finally, acetonitrile was investigated but no desired product was observed (Table 9,

entry 5). Presumably more polar solvents disrupt the H-bonding between the thiourea and substrates preventing any desired reaction.

Table 9. Solvent screen for asymmetric reductive nitro-Mannich reaction



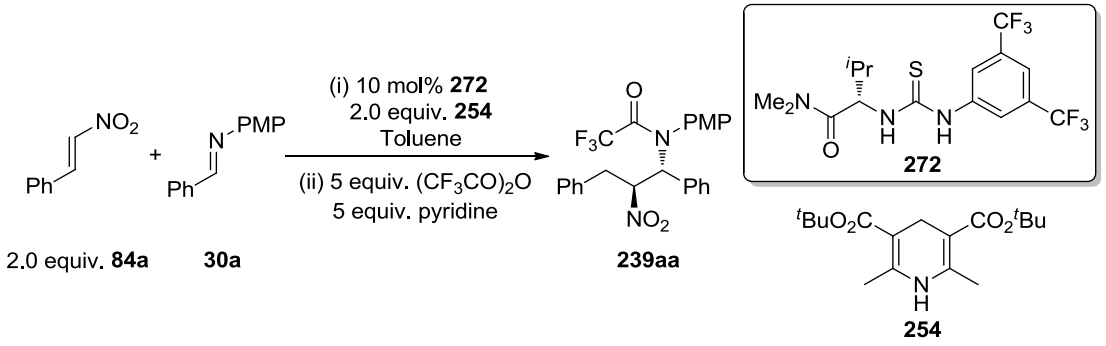
Entry	Solvent	Yield[a] of 239aa	*dr*[b] of 239aa	% *ee*[c] of 239aa
1	Toluene	75	90:10	90
2	CH_2Cl_2	70	90:10	90
3	Et_2O	70	90:10	16
4	THF	13	90:10	94
5	MeCN	<5	n.d.	n.d.

[a] Isolated yield of **239aa**. [b] Calculated from ^{1}H NMR . [c] Determined by chiral HPLC.

After confirming toluene as the ideal solvent the effects of the reaction time and temperature were investigated (Table 10). Initially the reaction was monitored by ^{1}H NMR and it was observed that the reaction had reached completion after only 30 minutes. When the reaction was then subjected to the protection conditions after this time, **239aa** could be isolated with a slightly increased 94% *ee* (Table 10, entry 2). As had been observed with Jacobsen's catalyst (Table 7), extended reaction times led to erosion of enantioselectivity presumably *via* retro-addition and the uncatalysed background nitro-Mannich reaction. In an attempt to limit or prevent this retro-addition reaction the temperature of the reaction was lowered. At 0 ^{o}C, the reaction reached completion after 6 h and **239aa** could be isolated in 95% *ee* and as a single diastereomer (Table 10, entry 3). Further decreasing the temperature gave further slight improvements giving **239aa** in 97% *ee* after 14 h at -10 ^{0}C and in 98% *ee* after 20 h at -20 ^{o}C (Table 10, entries 4-5). It was felt that although further decreasing the temperature may lead to higher enantioselectivity, reaction times greater than one day would be undesirable so -20 ^{o}C was selected as the chosen

temperature to investigate the full reaction scope. Finally, the reaction was left at -20 ^{o}C over several days to confirm that no erosion of enantioselectivity would be observed at this temperature and after 3 days at -20 ^{o}C **239aa** could still be isolated in 98% *ee* (Table 10, entry 6).

Table 10. Investigating the effect of reaction time and temperature



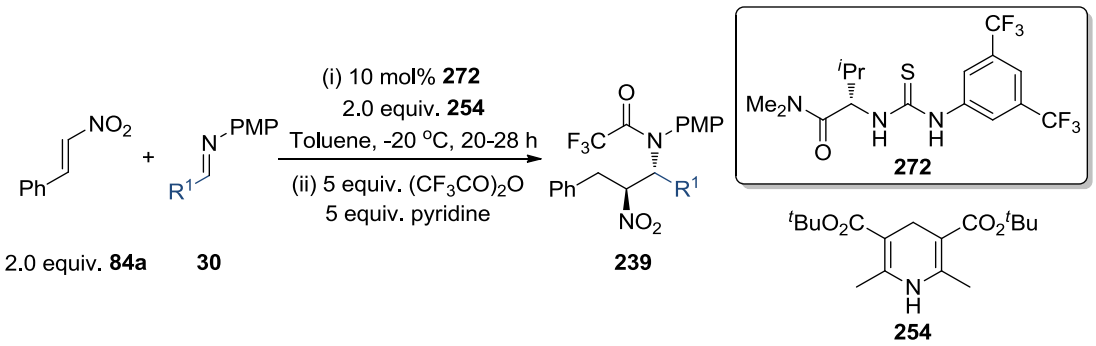
Entry	Rxn. time[a]	Temp.	Yield[b] of 239aa	*dr*[c] of 239aa	% *ee*[d] of 239aa
1	2 h	rt	75	90:10	90
2	30 min	rt	74	90:10	94
3	6 h	0 ^{o}C	70	>95:5	95
4	14 h	-10 ^{o}C	78	>95:5	97
5	20 h	-20 ^{o}C	81	>95:5	98
6	72 h	-20 ^{o}C	83	>95:5	98

[a] Reaction time for part (i). [b] Isolated yield of **239aa**. [c] Calculated from ^{1}H NMR . [d] Determined by chiral HPLC.

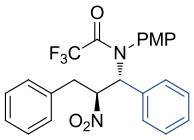
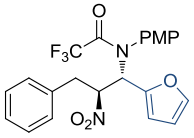
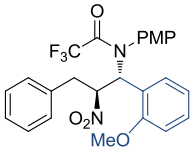
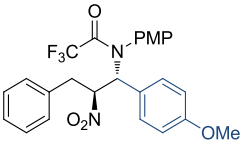
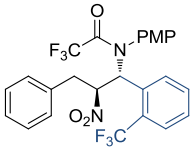
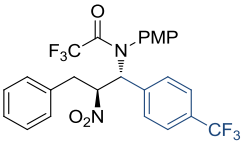
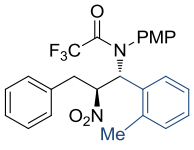
2.2.4 Investigation of the reaction scope

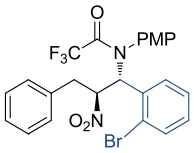
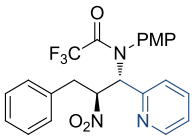
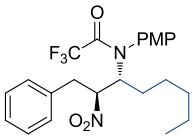
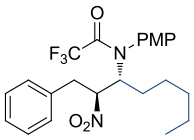
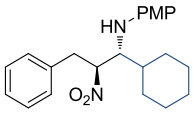
With optimised conditions for the reaction with catalyst **272** in hand, the scope of the reaction with respect to imines was investigated (Table 11). The reaction worked well for a variety of aromatic and heteroaromatic imines, furyl imine **30b** gave the desired product in a 77% yield, in 97% *ee* and as a 90:10 mixture of diastereomers (Table 11, entry 2). The reaction also worked well with electron rich aromatic groups producing the products in near enantiopurity (Table 11, entries 3-4). Electron deficient aromatics were less consistent as when the imine was substituted with a trifluoromethyl group in the *ortho* position, **239af** was formed in an 80:20 diastereomeric ratio.

Table 11. Scope of asymmetric reductive nitro-Mannich reaction with respect to imine



2.0 equiv. **84a** **30** **239**

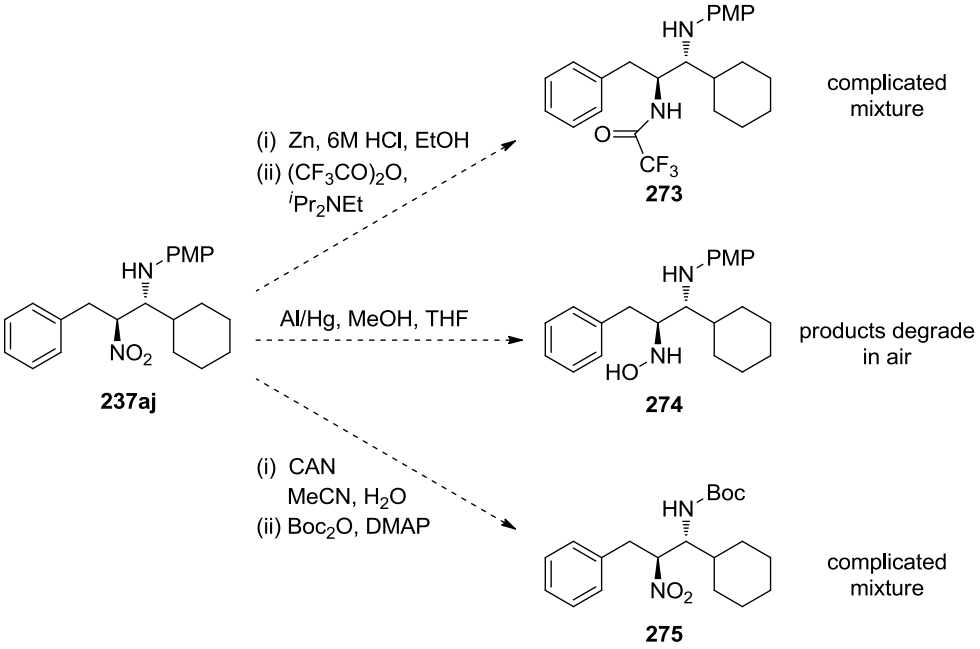
Entry	R^1		Yield[a]	*dr*[b]	% *ee*[c]	Final product	
1	Phenyl	**30a**	81	>95:5	98		**239aa**
2	2-Furyl	**30b**	77	90:10	97		**239ab**
3	2-MeO-C_6H_4	**30c**	83	>95:5	99		**239ac**
4	4-MeO-C_6H_4	**30e**	75	>95:5	97		**239ae**
5	2- F_3C-C_6H_4	**30f**	66	>95:5 (80:20)	80 (4)		**239af**
6	4-F_3C-C_6H_4	**30g**	74	90:10	94		**239ag**
7	2-Tolyl	**30h**	75	>95:5 (85:15)	90 (34)		**239ah**

8	2- Br-C_6H_4	**30r**	70	>95:5 (80:20)	92 (10)		**239ar**
9	2-Pyridyl	**30k**	76	>95:5	96		**239ak**
10	^{n}Pentyl	**30i**	30	>95:5	75		**239ai**
11[d]	^{n}Pentyl	**30i**	59	>95:5	73		**239ai**
12	Cyclohexyl	**30j**	45	>95:5 (65:35)	n.d.		**237aj**

[a] Isolated yield of **239**. [b] *dr* of isolated **239** calculated from ^{1}H NMR. Parentheses indicate *dr* of crude **239**. [c] % *ee* of isolated **239** determined by chiral HPLC. Parentheses indicate % *ee* of isolated *syn* diastereomer. [d] Reaction was performed at room temperature for 1 h.

These could be separated by column chromatography to yield 66% of the *anti* diastereomer in an 80% *ee* (Table 11, entry 5). The *para* substituted analogue **239ag** however was formed in a 74% yield as a 90:10 *dr* and in 94% *ee* (Table 11, entry 6) suggesting that the lower diastereo- and enantioselectivity observed with *ortho*-CF_3 analogue **239af** is not due to electronic effects. The result obtained using *ortho*-tolyl substituted imine **30h** suggested that sterics may be responsible for the low stereoselectivity as **239ah** was also formed as a diastereomeric mixture (85:15 *dr*) but with an improved enantiopurity of 90% *ee* (Table 11, entry 7). That the trifluoromethyl group (A-value – 2.1)[133] is slightly larger than a methyl group (A-value – 1.7)[133] is supportive of such a steric effect. The *ortho*-bromo substituted analogue **239ar** also formed as a mixture of diastereomers (80:20 *dr*) and in 92% *ee* (Table 11, entry 8). Interestingly, as these three *ortho*-substituted analogues were only formed with moderate diastereoselectivity, it enabled isolation and determination of the enantiopurity of the minor *syn* diastereomers. In each case the *syn* diastereomers were found to be considerably less enantioenriched compared to their *anti* counterparts (Table 11, entries 5,7 and 8). This suggests that the *syn*

diastereomers are being formed *via* an alternative reaction mechanism to the *anti* diastereomers. Pleasingly, 2-pyridyl analogue **239ak** was also formed with excellent levels of stereocontrol (>95:5 *dr*, 96% *ee*) and in 76% yield (Table 11, entry 9). The high diastereoselectivity of this example was particularly encouraging as in the previously described racemic synthesis this analogue was formed as a 75:25 mixture of diastereomers (see section 2.1.2, Table 5). Finally, alkyl imines **30i** and **30j** were examined in the reaction. Unfortunately, due to the instability of ^{n}pentyl substituted imine **30i** the desired product was only formed with a low yield of 31% (Table 11, entry 10). However, it was discovered that by conducting the reaction at room temperature, the reaction could be completed before significant degradation of imine **30i** occurred to form **239ai** in a 59% yield and in 73% *ee* (Table 11, entry 11). As of yet, it is unknown as to why ^{n}pentyl substituted imine **30i** gives **239ai** with only moderate enantioenrichment. Cyclohexyl imine **30j** was also examined in the reaction, and as previously noted in the racemic reaction (see section 2.1.2, Table 5), the reaction was poorly diastereoselective (65:35 *dr*) and trifluoroacetamide protection could not be performed (Table 11, entry 12).



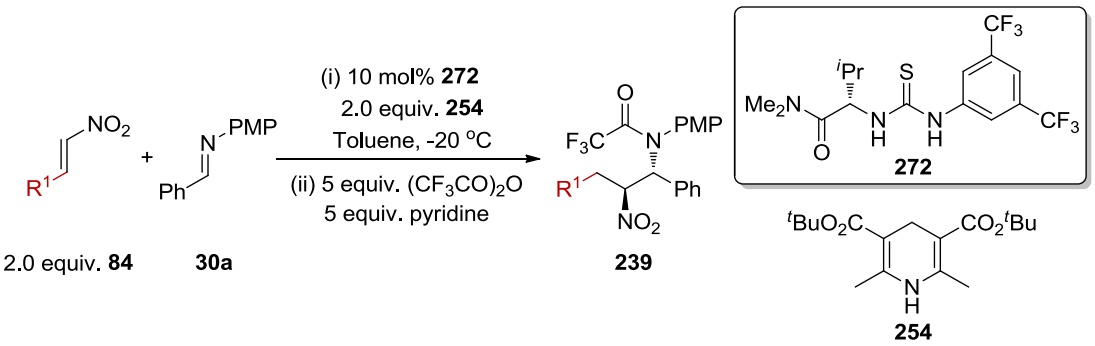
Scheme 103. Attempts to form stable analogue of **237aj**

Unfortunately, although **237aj** could be isolated by column chromatography as a single diastereomer, degradation was observed whilst analysing the product by chiral HPLC, preventing measurement of the enantiopurity. Several methods were attempted to synthesise a more stable product from the nitro-Mannich reaction using

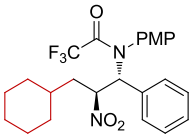
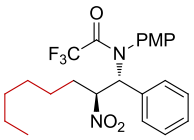
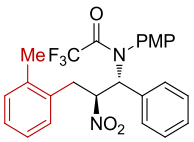
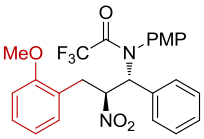
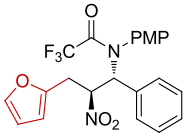
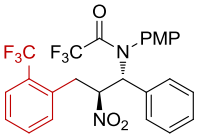
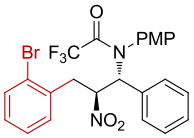
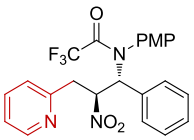
cyclohexyl imine **30j**, but no success was achieved (Scheme 103). Reduction of *β*-nitroamine **237aj** using zinc dust and hydrochloric acid gave a complex mixture of products that could not be separated by chromatography. Attempted reduction to hydroxylamine **274** using an aluminium amalgam appeared to succeed but the product was unstable in air and rapidly degraded. Finally, deprotection of the *para*-methoxy phenyl group using ceric ammonium nitrate (CAN) followed by *N*-Boc protection also gave a complicated mixture of products.[134]

The scope of the reaction with respect to nitroalkenes was also examined (Table 12). Initially, alkyl substituted nitroalkenes **84b** and **84c** were investigated and pleasingly, desired products **239ba** and **239ca** were formed in excellent yields (75% and 71% respectively), and with excellent levels of stereocontrol (>95:5 *dr*, 95% *ee* and 97% *ee* respectively) for both analogues (Table 12, entries 1-2). Electron rich nitroalkenes however, were less successful. As the electron donating ability of the substituent increases, much longer reaction times were required to complete the reaction. This is best exemplified with furyl nitroalkene **84d** where the reaction took 10 days to reach completion (Table 12, entry 5). Additionally the reaction yield was also greatly reduced in these examples as the reduction of *N*-PMP imine **30a** became more competitive. Despite these poor yields, the diastereo- and enantioselectivity of these reactions remained excellent (Table 12, entries 3-5). Nitroalkenes bearing electron withdrawing substituents worked well in the reaction giving the desired products in excellent yields and with excellent diastereo- and enantiocontrol (Table 12, entries 6-7). Pyridyl analogue **84k** was also successful in the reaction forming **239ka** in a 68% yield with a >95:5 *dr* and in 98% *ee* (Table 12, entry 8). Overall, the reaction exhibited excellent stereocontrol with all nitroalkenes tested, presumably the substituents are too far away from the reacting centre to have an effect on the enantioselectivity of the reaction. The slow reactions with a number of electron rich nitroalkenes suggested that the rate limiting step of the reaction is the reduction of the nitroalkene.

Table 12. Scope of asymmetric reductive nitro-Mannich reaction with respect to nitroalkene



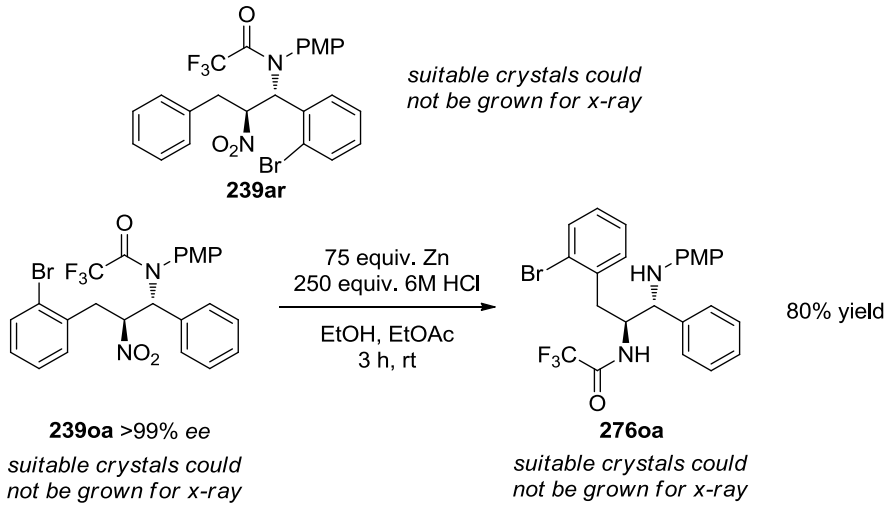
2.0 equiv. **84** **30a** **239**

Entry	R^1		Rxn. time	Yield[a]	*dr*[b]	% *ee*[c]	Final product	
1	Cyclohexyl	**84b**	20 h	75	>95:5	95		**239ba**
2	^{n}Pentyl	**84c**	20 h	71	>95:5	97		**239ca**
3	2-Tolyl	**84e**	48 h	70	>95:5	98		**239ea**
4	2-MeO-C_6H_4	**84g**	72 h	64	>95:5	98		**239ga**
5	2-Furyl	**84d**	240 h	32	>95:5	95		**239da**
6	2-F_3C-C_6H_4	**84i**	20 h	73	>95:5	95		**239ia**
7	2-Br-C_6H_4	**84o**	20 h	79	>95:5	98		**239oa**
8	2-Pyridyl	**84k**	28 h	68	>95:5	98		**239ka**

[a] Isolated % yield of **239**. [b] *dr* of isolated **239** calculated from ^{1}H NMR. [c] % *ee* of isolated **239** determined by chiral HPLC.

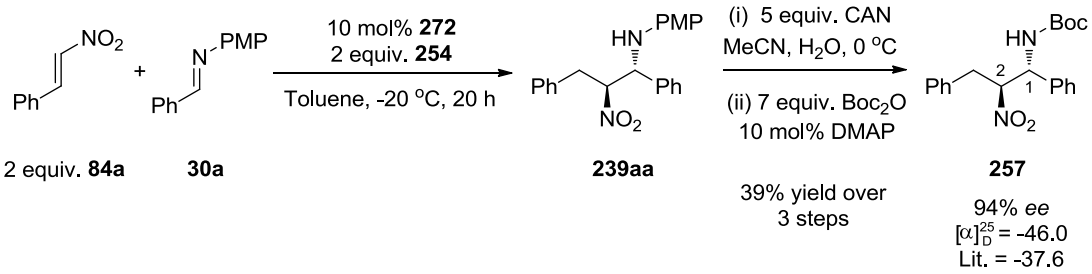
2.2.5 Determination and origin of absolute stereochemistry

Initially, it was attempted to determine the absolute stereochemistry by single X-ray crystallography. Unfortunately, attempts to form suitable crystals of *β*-nitrotrifluoroacetamides containing heavy atoms such as bromo-substituted analogues **239oa** and **239ar** were unsuccessful. Although crystals could be grown, they formed as extremely thin needles. Suitable crystals also could not be grown with reduced product **276oa** either (Scheme 104).



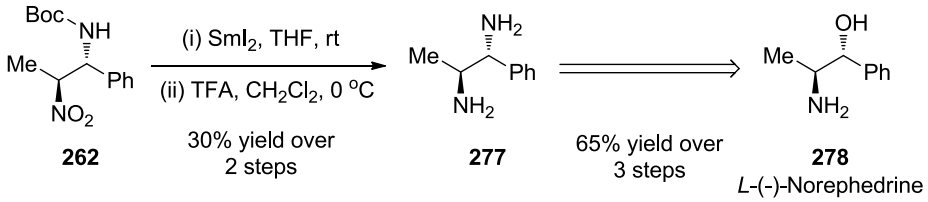
Scheme 104. Attempts to grow crystals for X-ray crystallography

Eventually it was discovered that the *para*-methoxy phenyl protecting group could be cleaved from *β*-nitroamine **239aa** and an *in-situ* Boc protection could be performed to produce literature compound **257** in a 39% yield from imine **30a**. The optical rotation of this product matched the literature value,[36] giving some evidence that product **239aa** from the reductive nitro-Mannich reaction has the 1*R*,2*S* stereochemistry. The other *β*-nitrotrifluoroacetamides synthesised (Table 11 and table 12) have been assigned the same stereochemistry by analogy.



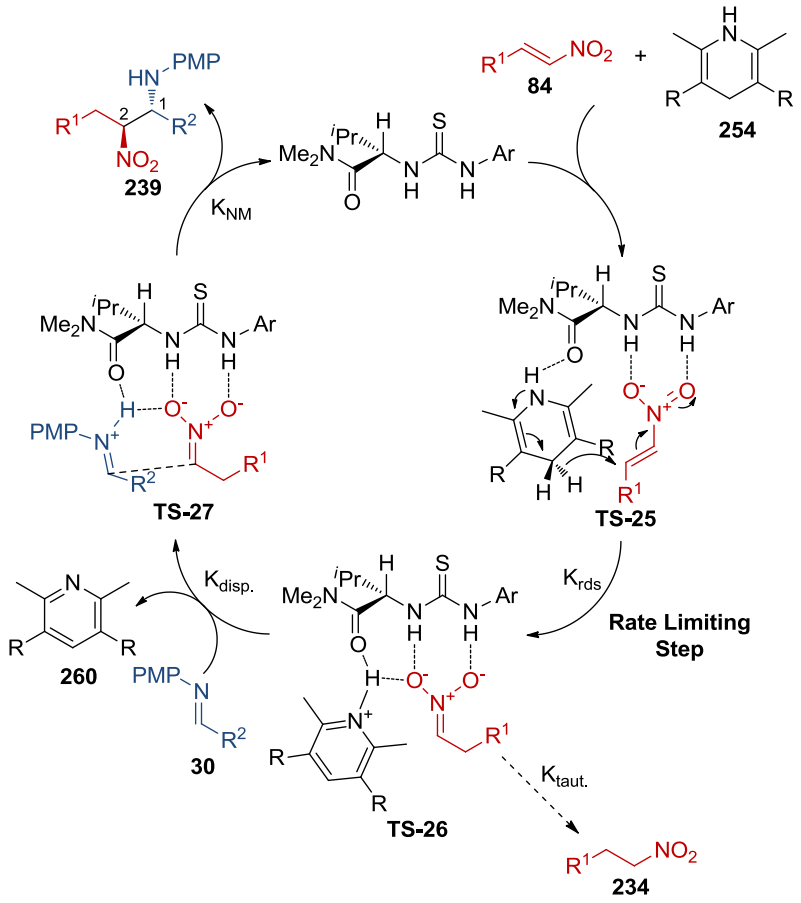
Scheme 105. Confirmation of absolute stereochemistry through comparison

This assignment of the absolute stereochemistry is not definitive however, as the original literature assignment of **257** was also determined by analogy based on the assignment of **262** which could also be formed by a nitro-Mannich reaction.[31,36] The assignment of **262** as 1*R*,2*S* was based on comparison with literature compound (1*R*,2*S*)-1,2-diamino-1-phenylpropane **277** which itself was synthesised from (1*R*,1*S*)-*L*-(−)-Norephedrine **278** (Scheme 106).[135]



Scheme 106. Literature assignment of **257** based on comparison to **262**

With the absolute stereochemistry now tentatively assigned, thoughts were turned towards the mechanism of the reaction and the enantiodetermining step. Firstly reduction of the nitroalkene occurs. Presumably, the amide group of the catalyst directs the attack of the hydride from the top face, as drawn in **TS-25** (Scheme 107), although this is inconsequential in this example. This is based on List's work where a similar amide containing catalyst **191** directs the face of the hydride's attack in a similar fashion (see section 1.3.4).[102] The results from optimising the stoichiometry of the reaction, where the rate of reaction was insensitive to an excess of imine, and increasing rate of reaction with increasing stoichiometry of nitroalkene and Hantzsch ester were observed (see section 2.2.1); as well as a slower rate of reaction with more electron rich nitroalkenes, (Table 12) suggest that the reduction is the rate limiting step. It is thought that after reduction, the nitronate must react with an imine almost instantaneously as no reduced nitroalkene **234** is typically observed until complete consumption of imine **30** has occurred. Presumably, due to the greater basicity of *N*-PMP imine **30** and the large size of the pyridinium species, rapid displacement occurs and six-membered transition state **TS-27** is formed suggesting that $k_{disp.} >> k_{taut.}$. This then collapses to give *anti* diastereomer **239** with the (1*R*, 2*S*) stereochemistry (Scheme 107).



Scheme 107. Proposed reaction mechanism for the tandem reductive nitro-Mannich reaction

It is thought that the enantioselectivity of this reaction is determined in the six-membered transition state **TS-27**. Before discussing this, it is important to consider the lowest energy conformation of the catalyst as this is likely to be similar to the conformation during the enantiodetermining step. Jacobsen's thiourea **153**, used in asymmetric Strecker reactions, possesses a similar structure to catalyst **272** and extensive experimental and theoretical calculations have been performed on this catalyst (Figure 22).[84]

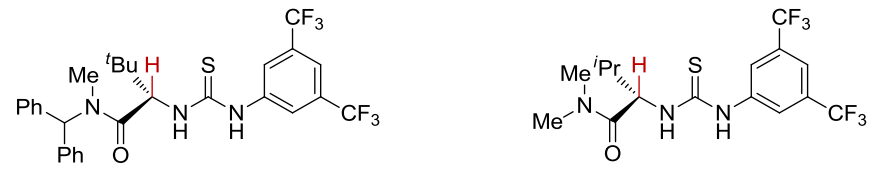


Figure 22. Comparison between **272** and catalyst for Strecker reaction

In these computational calculations, **153** exists with the highlighted C-H bond in the same plane as the C=S bond. This is presumably to minimise steric interactions

between the large sulfur atom and the amide or *tert*-butyl group. If we assume that catalyst **272** will adopt a similar conformation for the same reasons, then one of two likely transition states should be favoured (Figure 23).

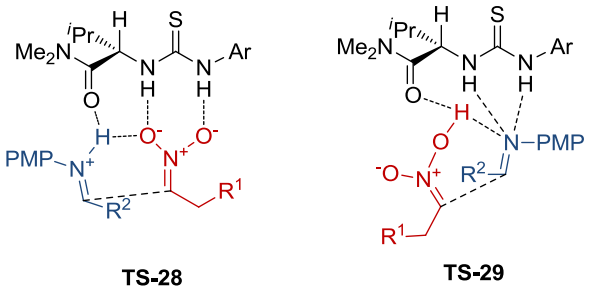


Figure 23. Two possible reaction transition states

In **TS-28**, the thiourea H-bonds to the nitronate species and the iminium species is H-bonded to the amide. Conversely, this could be the opposite way round as in **TS-29**, as imines are known to be stronger H-bond acceptors than nitro groups.[136] Although this is indeed a possible scenario it is thought to be less likely because several previous computational studies have found that the lower energy transition state involves the thiourea binding to the anionic (nucleophilic) reaction partner.[84,95,111] Additional support is given to **TS-28** from Jacobsen's work on the asymmetric Strecker reaction as the authors calculate lower energy transition states when the imine is H-bonded to the amide, as shown in **TS-28**, rather than the thiourea moiety of the catalyst (see Figure 9, section 1.3.3).[84] This information was combined with the suggested transition states for the racemic reaction to give proposed enantiodetermining conformations in figure 24.

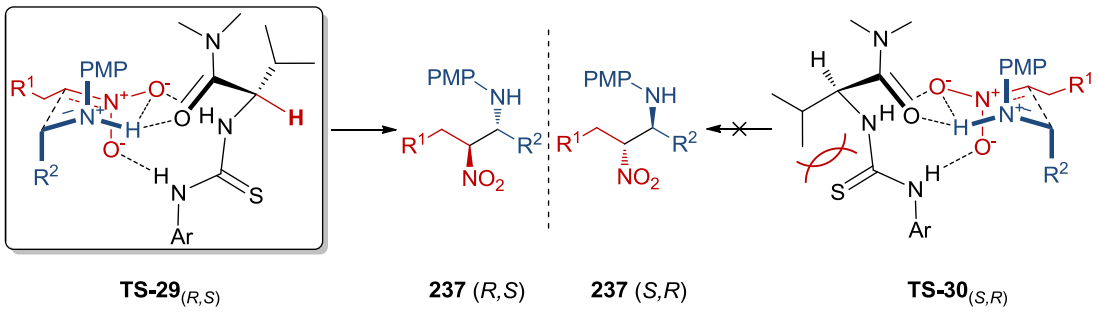


Figure 24. Proposed transition states for enantioselective reductive nitro-Mannich reaction

In **TS-29** the catalyst is in its lowest energy conformation (with the highlighted C-H bond in the same plane as the C=S bond), this allows the amide moiety of the catalyst to hydrogen-bond to the imine in a *pseudo* equatorial position stabilising the transition state. In **TS-30** in order for the amide moiety to H-bond in a *pseudo*

equatorial fashion, the large *iso*-propyl group has to be in the same plane as the large sulfur atom which is unfavourable. Another possible transition state would involve the amide moiety H-bonding to the imine in a *pseudo* axial position. In such a transition state **TS-32** looks of lower energy than **TS-31** as the C-H bond is in the same plane as the C=S bond (Figure 25). However, as the H-bond is in a *pseudo* axial position to R^2 it is anticipated that there would be a steric penalty compared to **TS-29** and as such **TS-32** is likely to be of higher energy.

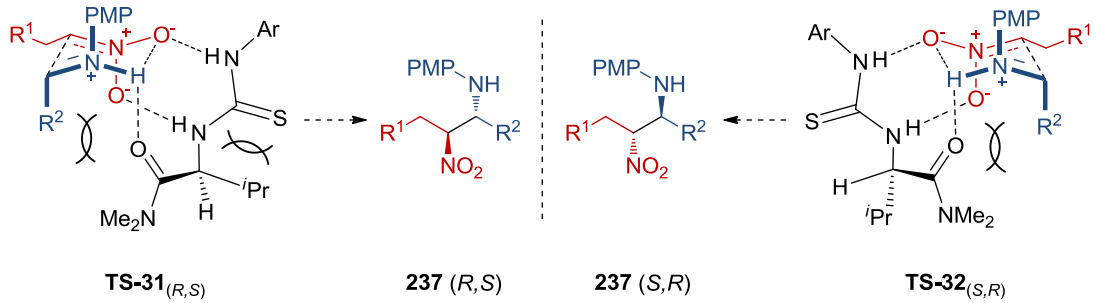


Figure 25. *Pseudo* axially H-bonded transition states

With a transition state model for the formation of the *anti* diastereomer proposed, attention was turned towards proposing a cause for the poor enantioselectivity observed in the *syn* diastereomers which were formed in some examples. When *N*-PMP imine **30** was substituted in the *ortho* position with a CF_3, Me or Br. group the reactions were only moderately diastereoselective and the enantioselectivity was poor for the *syn* diastereomer (Table 11, entries 5, 7 and 8). This low enantioselectivity suggests that the *syn* diastereomer is formed *via* an alternative transition state. In keeping with the proposed transition states for the racemic reaction, the *syn* diastereomer could be formed by a cyclic transition state where all substituents are in *pseudo* axial positions (see section 2.1.3). Due to the unfavourable steric interactions in such a transition state this seems unlikely so an acyclic transition state may be in operation. In such a transition state it would be very difficult for the amide moiety of the catalyst to also H-bond to the imine, preventing the catalyst from implementing high levels of stereocontrol for the *syn* diastereomer (Figure 26).

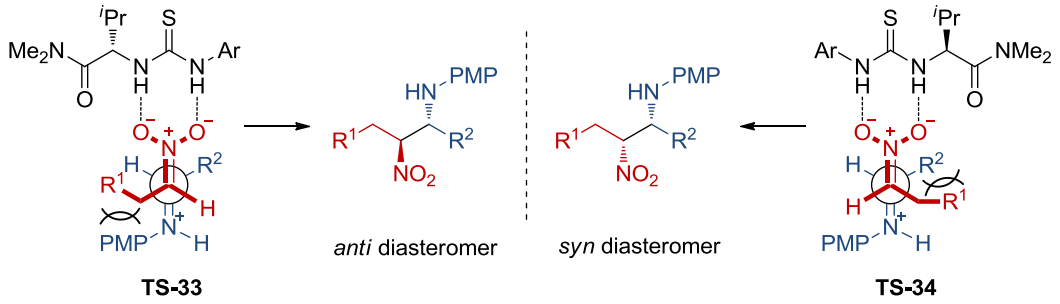


Figure 26. Acyclic transition states

Table 13 shows the calculated hydrogen bond basicities for a variety of hydrogen bond acceptors (HBA). Using this information, combined with the proposed transition state, we can begin to explain some of the observed differences in enantioselectivity of the reaction with different catalysts. Additionally, these ideas can be used to suggest new catalysts to synthesise to probe the mechanism further.

Table 13. Hydrogen-bond basicities of several small molecules

Entry	HBA	$-\Delta H^{o}$ (KJmol^{-1})[a] [136]	pK_{HB}[b]	β_2^{H}[c]
1	*N*,*N*-dimethylacetamide	29.2	2.44[137]	0.76[137]
2	*N*,*N*-dimethylbenzenesulfonamide	18.1	1.19[138]	0.49[138]
3	*N*,*N*-dimethylthioacetamide	20.0	1.32[139]	0.52[139]
4	Methyl acetate	20.8	1.00[140]	0.45[141]
5	1,1,3,3-tetramethylurea	28.6	2.44[137]	0.76[137]
6	1,1,3,3-tetramethylthiourea	-	1.35[139]	0.53[139]

[a] Enthalpy of H-bond with 4-fluorophenol in CCl_4. [b] Data taken from H-bond with 4-fluorophenol in CCl_4, $pK_{HB} = \log_{10}(K_{HB})$. [c] $\beta_2^{H} = (pK_{HB} + 1.1)/4.636$.

During the catalyst screen a large difference between the enantioselectivity achieved with catalyst **54** (Table 14, entry 1) and catalyst **266 (**Table 14, entry 2) was observed. Since it is now known that the diaminocyclohexane moiety is not responsible for the high enantioselectivity, it suggests that the acetyl group on catalyst **54** was responsible for the low stereoselectivity. Amides are typically stronger HBAs (Table 13, entry 1) than sulfonamides (Table 13, entry 2) so its plausible that with catalyst **54** the acetyl group on the diaminocyclohexane can form a H-bonded transition state that is competitive with the proposed transition state **TS-35** (Figure 27). The sulfonamide must form a weaker H-bond so is not as competitive and hence the enantioselectivity is higher. That catalyst **270** (Table 14, entry 3) forms the opposite enantiomer gives

some credence to this idea as it suggests that when the diaminocyclohexane is the only chiral group on the catalyst, a transition state similar to **TS-38** is in operation.

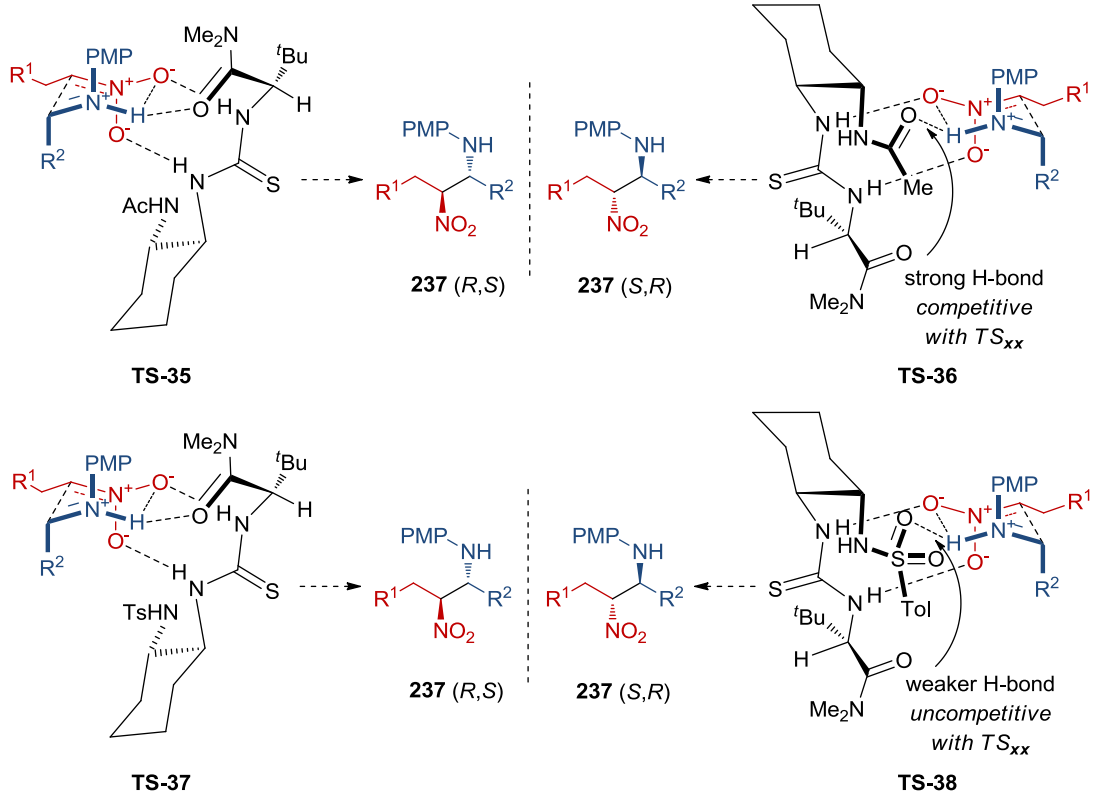
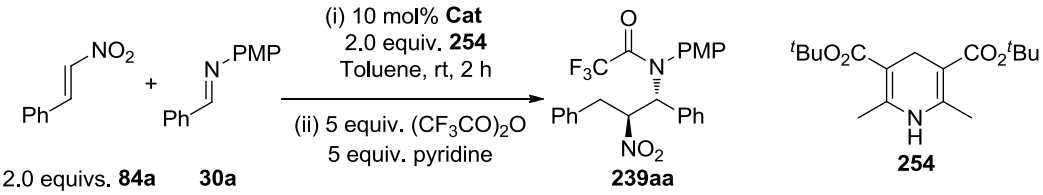


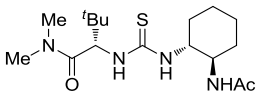
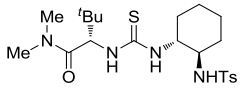
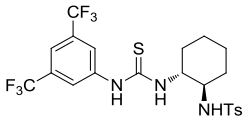
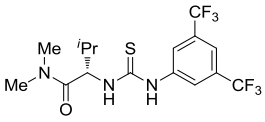
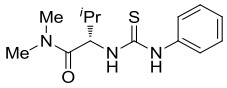
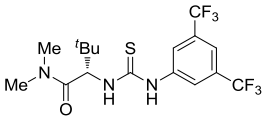
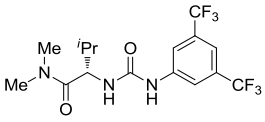
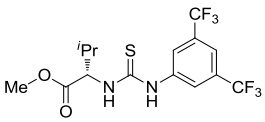
Figure 27. Competitive and uncompetitive transition states with catalysts **54** and **266**

To further probe the mechanism of this reaction some more catalyst structures were synthesised and examined in the reductive nitro-Mannich reaction, these along with selected examples from the earlier catalyst screen are shown in table 14. Although, no reaction rates were measured absolutely, it is thought that the reduction of the nitroalkene is the rate limiting step of the reductive nitro-Mannich reaction. As such the amount of *β*-nitrostyrene **84a** consumed in each example can be used as crude indicator of the rate of reaction for each catalyst. Although, this data should not be extrapolated too far, it should be sufficient to identify the more active catalyst. The first new catalyst synthesised was thiourea **279** where the bis-trifluoromethylbenzene group was substituted for a phenyl ring (Table 14, entry 5), as expected no difference in the stereoselectivity was observed but the relative rate of reaction was slightly reduced as indicated by comparing the amount of reduction of *β*-nitrostyrene **84a** with thiourea **272** (Table 14, entry 4).

Table 14. Further probing of the reaction mechanism with different catalysts

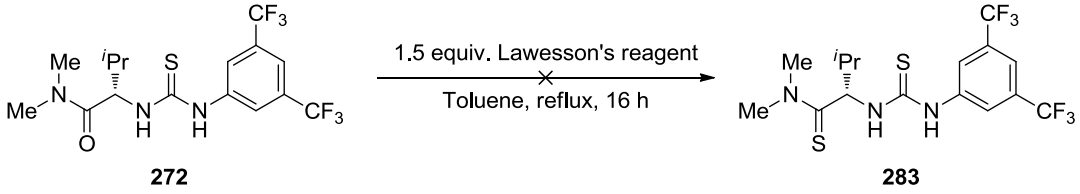


2.0 equivs. **84a** **30a** **239aa** **254**

Entry	Catalyst		%Conv.[a] of 84a	%Conv.[b] to 239	Yield[c] of 239	*dr*[b] of 239	% *ee*[d] of 239
1		**54**	75	90	77	95:5	50
2		**266**	40	55	48	>95:5	90
3		**270**	55	60	36	95:5	-64
4		**272**	85	90	75	90:10	90
5		**279**	60	95	72	90:10	90
6		**280**	50	70	62	90:10	94
7		**281**	90	95	70	90:10	90
8		**282**	45	70	53	90:10	92

[a] Calculated from ^{1}H NMR. As reduction of nitroalkene **84** is rate limiting step, this value can be thought of as a crude indicator of the rate of reaction. [b] Calculated from ^{1}H NMR before trifluoroacetamide protection. [c] Isolated yield of **239aa**. [d] Determined by chiral HPLC.

The slower relative rate of reaction in this case is not surprising as phenyl thiourea **279** should be a weaker H-bond donor than **272** bearing a bis-trifluoromethylbenzene group. Next, *tert*-butyl substituted catalyst **280** was tested in the reaction. A slight increase in the enantioselectivity of the reaction was noticed with **239aa** isolated in 94% *ee* (Table 14, entry 6) compared to *iso*-propyl substituted catalyst **272** (Table 14, entry 4) suggesting that the bulkier *tert*-butyl group results in a more selective reaction. However, the relative rate of reaction with this catalyst was slower than the reaction with catalyst **272**. This could explain the higher enantioselectivity as less retro-addition may have occurred, as when the reaction with catalyst **272** was stopped after 30 min desired product **239aa** was also formed in 94% *ee* (Table 10, entry 2, see section 2.2.3). Urea catalyst **281** was also investigated and also delivered **239aa** in 90% *ee* (Table 14, entry 7). This result suggests that the thio(urea) moiety of the catalyst is acting as a H-bond donor rather than a H-bond acceptor. Unexpectedly, the relative rate of reaction using urea **281** was also very similar to that observed with thiourea **272**. Finally, it was thought that a good way to probe the idea of a key H-bond between the amide of the catalyst and the iminium species would be to make either a thioamide or ester containing catalyst as both these functional groups are weaker HBAs (compare entries 1,3 and 4, table 13) than dimethylamide and should result in weaker binding and hence a lower enantioselectivity for the reaction. It was attempted to synthesise thioamide catalyst **283** using Lawesson's reagent, but unfortunately, no desired product was obtained from the reaction (Scheme 108). As a result, the reductive nitro-Mannich reaction using methyl ester catalyst **282**, which was synthesised from the commercially available *L*-valine methyl ester, was performed. Interestingly, the reaction formed **239aa** in excellent enantiopurity (92% *ee*) albeit in only a moderate yield of 53% (Table 14, entry 8). This result was also unexpected as the methyl ester of **282** should not be able to form as strong a H-bond with the iminium species as the dimethylamide moiety (Table 13, entries 1 and 4). This final result suggests that the enantiodetermining step is more complex than previously thought.

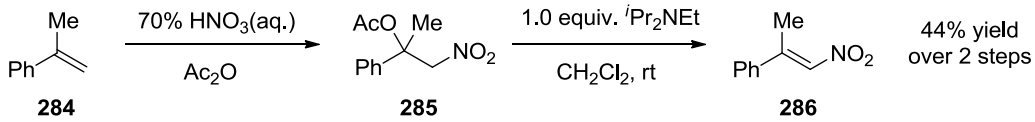


272 **283**

Scheme 108. Attempt to form thioamide catalyst

2.2.6 Forming three contiguous stereocentres

One of the possibilities that prompted the examination of a reductive nitro-Mannich reaction was the potential to synthesise molecules with three contiguous stereocentres by using *α*-substituted-*β*-nitrostyrenes as the starting nitroalkene. A few preliminary experiments towards this aim have been performed and this section will briefly discuss these results. Nitroalkene **286** was synthesised from *α*-methylstyrene by nitration in acetic anhydride followed by elimination to give **286** in 44% yield over two steps. This method was chosen as Henry reactions of ketones are typically low yielding.[142]



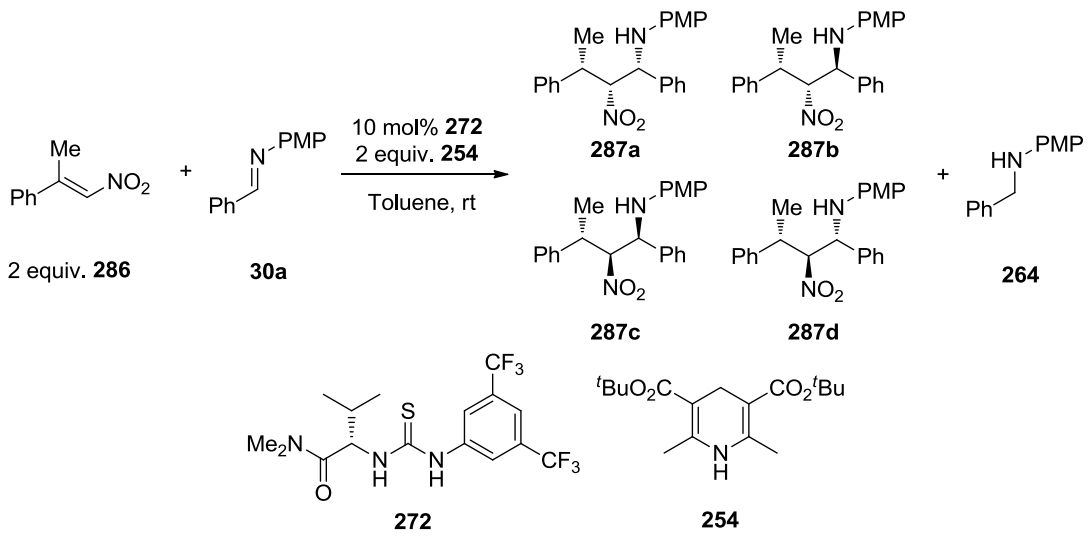
284 **285** **286**

Scheme 109. Synthesis of *α*-methyl-*β*-nitrostyrene

With nitroalkene **286** in hand the reductive nitro-Mannich reaction was examined using two equivalents of nitroalkene **286** and two equivalents of Hantzsch ester **254** and 10 mol% thiourea **272** as catalyst. The reaction was monitored by ^{1}H NMR with small aliquots taken from the reaction at three different intervals (Table 15). It was immediately noticed that the reduction of nitroalkene **286** was significantly slower than with *β*-nitrostyrene **84a** as only 10% conversion to the desired product was observed after 30 min. With **84a**, complete conversion to the desired product had occurred by this point. Although, the reaction had only reached 10% conversion after 30 min the *dr* of the reaction could be determined and it was observed that *syn,anti* diastereomer **287b** was favoured (Table 15, entry 1). Interestingly, as the reaction was left to stir for longer the diastereoselectivity of the reaction altered to favour *syn,syn* diastereomer **287a** in a 65:5:30:0 ratio after 2h 30 min with 30% conversion **(**Table 15, entry 2). After stirring overnight, **287a** was favoured with a *dr* of 95:0:5:0 and 60% conversion (Table 15, entry 3). Unlike, the *anti* nitro-Mannich products

which have been synthesised for most of this research *syn*,*syn* product **287a** was stable to chromatography and could be isolated in 37% yield and 84% *ee*.

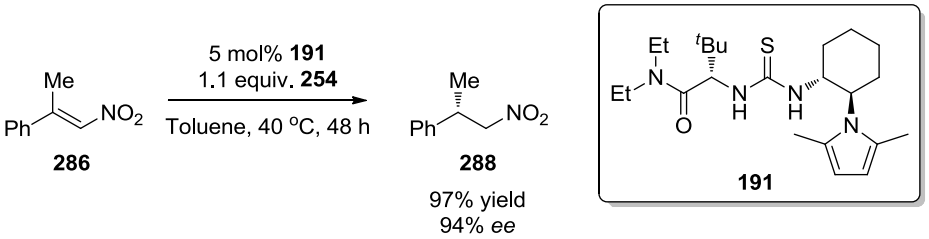
Table 15. Preliminary investigations into reaction forming 3 stereocentres



Entry	Rxn. time	% Conv[a] to 287	% Conv[a] to 264	*dr*[b] (a:b:c:d)	% Yield[c]	% *ee*[d]
1	30 min	10	10	10 : 80 : 10 : 0	n/a	n/a
2	2 h 30	30	35	65 : 5 : 30 : 0	n/a	n/a
3	17 h	55	45	95 : 0 : 5 : 0	37	84

[a] Calculated from ^{1}H NMR. [b] *dr* of crude reaction mixture, calculated from ^{1}H NMR. [c] Yield of isolated **287**. [d] % *ee* of isolated **287**, determined by chiral HPLC.

It should be pointed out that this level of enantioselectivity is very impressive considering the simplicity of the catalyst and that List's catalyst achieves a 94% *ee* for the reduction of the same nitroalkene, albeit at higher temperature (Scheme 110).[102]



Scheme 110. Reduction of nitroalkene **286** using List's thiourea

In addition to the high enantioselectivity several other interesting observations were made during this experiment. Firstly, the poor reactivity of nitroalkene **286** towards reduction can be explained by a steric argument. When nitroalkene **286** exists in its fully conjugated conformation **286a**, there is an unfavourable steric interaction between the methyl and the nitro group. Because of this clash, nitroalkene **286** is more likely to adopt conformation **286b** wherein the nitro group is not in conjugation with the styrene and hence the nitroalkene is a weaker electrophile (Figure 28). Such a problem does not exist in *β*-nitrostyrene **84a** where the *α*-substituent is a small hydrogen atom.

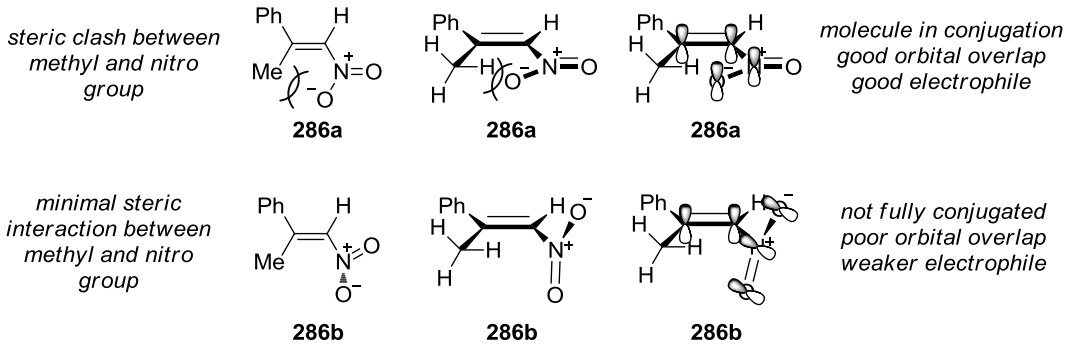


Figure 28. Explanation for poor reactivity of *α*-methyl-*β*-nitrostyrene

The observed stereochemistry of the reaction is also of great interest. The absolute stereochemistry was based on comparison of the $[\alpha]_D$ of **287a** with that previously observed when **287a** was synthesised by the Anderson group.[53] Additionally, nitroalkane **288**, obtained from reduction of nitroalkene **286** using thiourea **272**, matched the value obtained with List's catalyst revealing the (*S*) stereochemistry. The nitro-Mannich reaction that follows the reduction is then under substrate control rather than catalyst control as the stereochemistry of the desired product is the opposite (**287b** 1*S*, 2*R*, 3*S*) to what has been previously seen using catalyst **272** (1*R*, 2*S*, see section 2.2.5). The observed initial diastereoselectivity can be explained by the proposed transition states in figure 29. In transition state **TS-39** steric interactions are minimised resulting in the lowest energy and hence resulting in the observed *syn,anti* stereochemistry. When attempting to react the nitronate and imine under catalyst control (i.e. cyclic transition states **TS-40** or **TS-41**) unfavourable steric clashes exist (Figure 29). Of even greater interest than the reaction being under substrate control, is the changing diastereoselectivity over time.

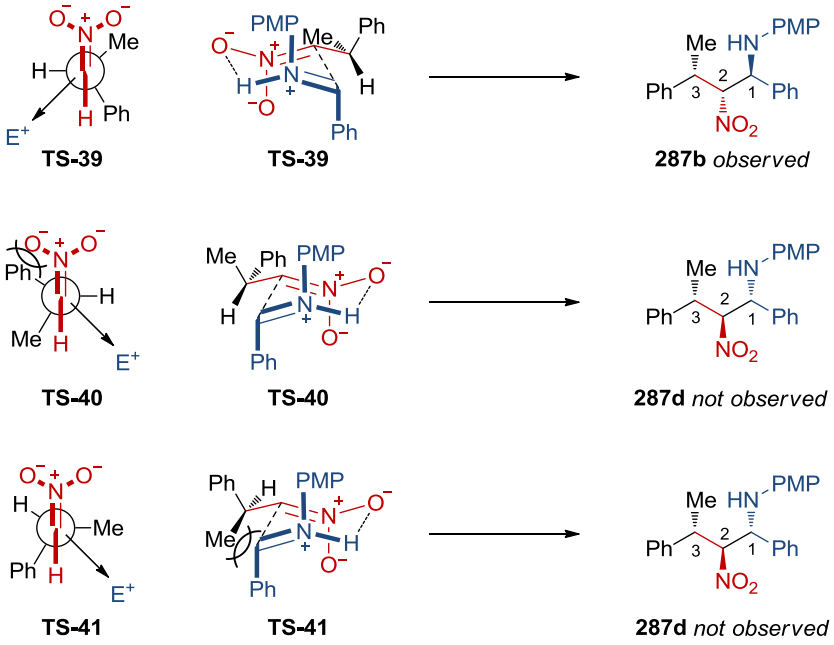


Figure 29. Transition state for initial observed stereochemistry

This suggests initial formation of kinetic *syn,anti* product **287b** which then converts to the thermodynamic *syn,syn* product **287a**. The idea that *syn,syn* product **287a** is the thermodynamic product becomes more clear when the *β*-nitroamines are drawn as H-bonded cyclic structures (Figure 30). In **287a** all of the substituents are in *pseudo* equatorial positions whereas in **287b** one substituent has to sit in a *pseudo* axial position creating unfavourable steric interactions.

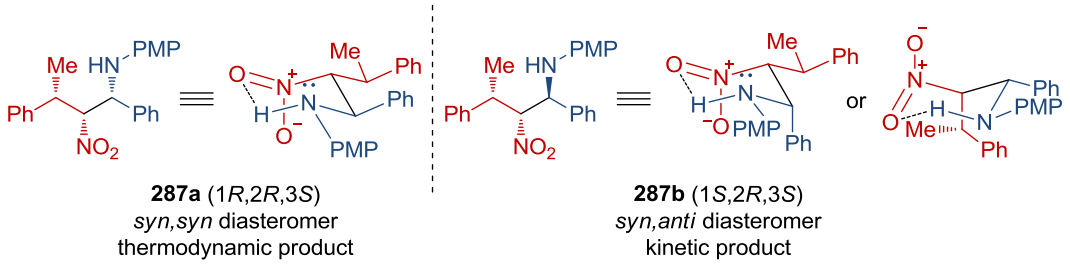
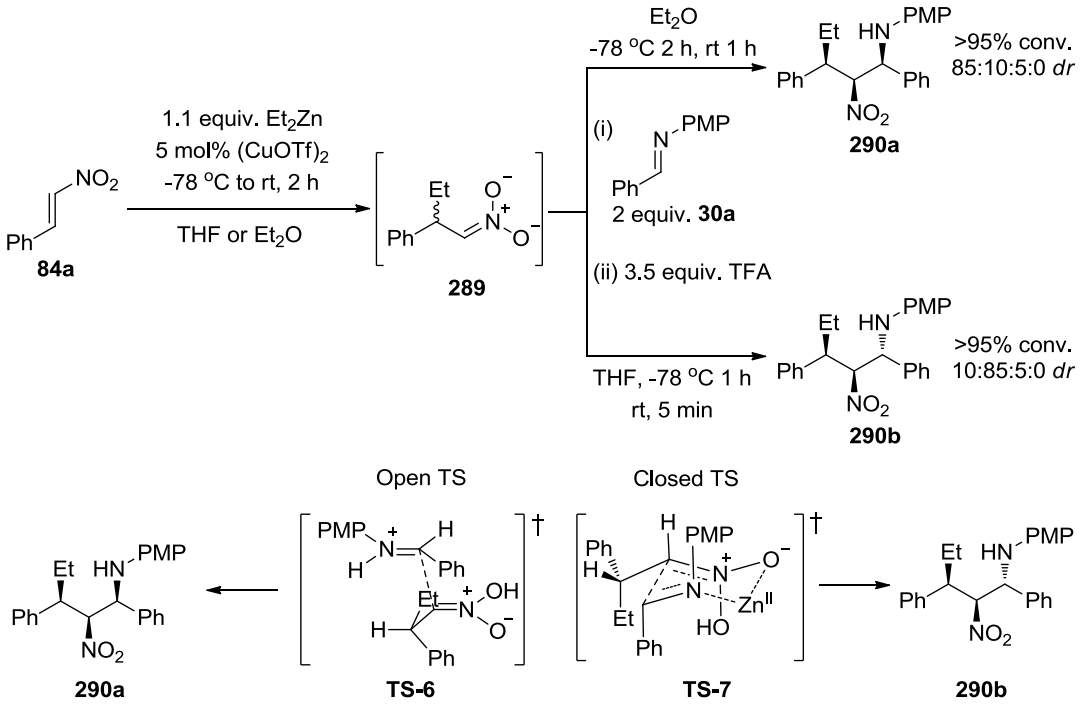


Figure 30. Chair conformation structures of **287a** and **287b**

It is proposed that the conversion from the kinetic to thermodynamic product occurs *via* a retro-addition/nitro-Mannich reaction sequence rather than by deprotonation, as catalyst **272** is already known to catalyse the retro-addition. In order to gain a better insight into this reaction it was compared to the conjugate addition/nitro-Mannich reactions using dialkyl zincs described by Anderson's group (see Scheme 111 for example).[53] In this work the choice of solvent used would either favour *syn,syn* diastereomer **290a** (when diethyl ether, toluene or dichloromethane were used as

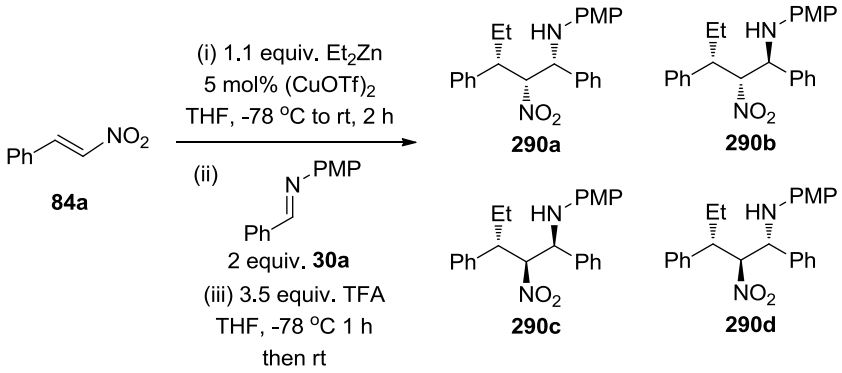
solvent), or *syn,anti* diastereomer **290b** (when tetrahydrofuran, dimethoxyethane or acetone). The authors attributed this difference to the role of zinc (II) trifluoroacetate which was precipitated during the reaction in diethyl ether, leading to a proposed open transition state. In tetrahydrofuran the reaction remained homogenous, suggesting the proposed closed transition state (Scheme 111).



Scheme 111. Conjugate addition/nitro-Mannich reaction using diethyl zinc

Intrigued by this research and keen to see if any similarities can be found between the mechanisms of the conjugate addition/nitro-Mannich reaction and the thiourea catalysed reductive nitro-Mannich reaction, some extra experiments were performed to examine the role of the zinc species in these reactions. Using the same conditions as the authors, a repeat of the reaction in tetrahydrofuran was performed but the products of the reaction were monitored using ^{1}H NMR. The reaction was sampled at regular intervals and produced some interesting results (Table 16). Although, the reaction favours *syn,anti* diastereomer **290b** initially (Table 16, entry 1), very quickly the reaction favours *syn,syn* diastereomer **290a** (Table 16, entries 2-6). These results are in close agreement to what was obtained using thiourea catalyst **272** in the reductive nitro-Mannich reaction (albeit with a methyl substituent, A-value = 1.7, rather than the similarly sized ethyl group, A-value = 1.75)[133]. This suggests that the zinc species (or possibly the copper (II) triflate) is catalysing the retro-addition in a similar fashion to thiourea **272**.

Table 16. Conjugate addition/nitro-Mannich reaction with diethyl zinc in THF

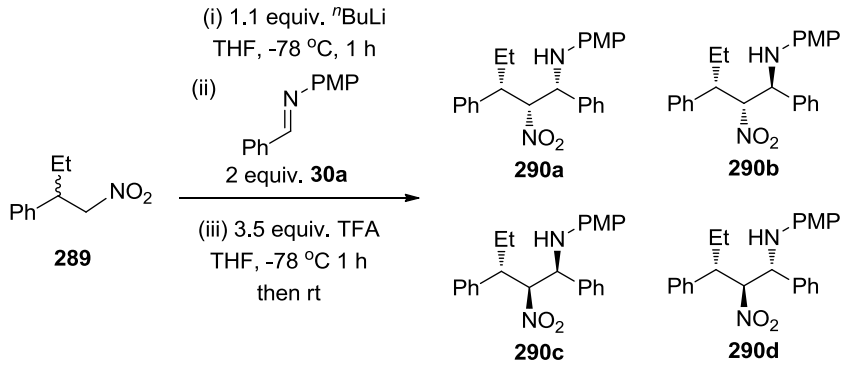


Entry	Time at rt	% Conv.[a]	*dr* (a:b:c:d)[b]
1	5 min	77	15:80:5:0
2	30 min	76	40:20:20:0
3	1 h	83	70:10:20:0
4	2 h	88	65:10:25:0
5	4 h 30 min	89	70:5:25:0
6	24 h	88	70:5:25:0

[a] % Conv. to **290** by ^{1}H NMR. [b] *dr* of crude **290** calculated from ^{1}H NMR.

To further support this idea a nitro-Mannich reaction using nitroalkane **289** was examined to ensure that the interconversion between diastereomers is a catalysed process (Table 17). As can be seen, although the reaction is gradually moving towards favouring *syn,syn* diastereomer **290a**, the rate at which this is occurring is significantly slower than that observed in the presence of the zinc species or with thiourea **272**.

Table 17. Effects of reaction time on nitro-Mannich reaction of nitroalkane **291**



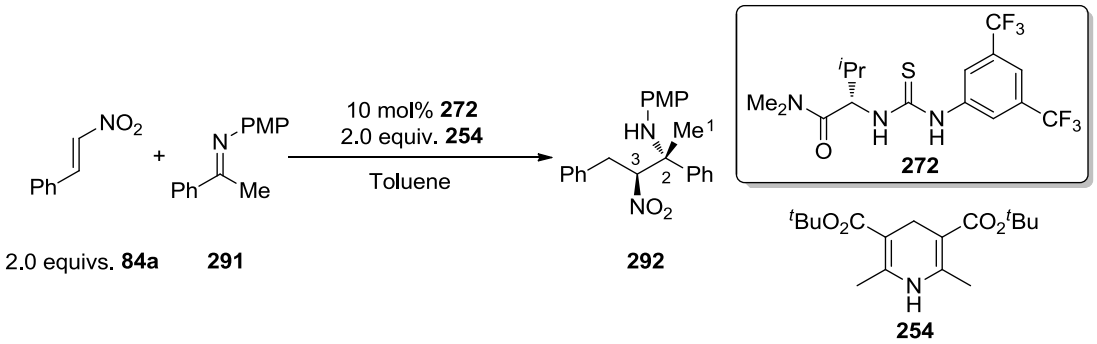
Entry	Time at rt	% Conv.[a]	*dr* (a:b:c:d)[b]
1	5 min	55	5:90:5:0
2	30 min	55	10:85:5:0
3	1 h	51	10:85:5:0
4	2 h	50	15:75:10:0
5	4 h 30 min	45	25:65:10:0

[a] % Conv. of **290** by ^{1}H NMR. [b] *dr* of crude **290** calculated from ^{1}H NMR.

2.2.7 Reaction with ketimines to form quaternary centres

Currently, there have been no reports of a general asymmetric nitro-Mannich reaction with ketimines so the ability of the thiourea catalysed reductive nitro-Mannich reaction to form quaternary centres has also been briefly investigated. Using *N*-PMP protected ketimine **291** the reaction was attempted initially at room temperature. After 1 h at this temperature 60% conversion to the desired product was observed with a *dr* of 75:25 (Table 18, entry 1). After an additional hour at this temperature the conversion to the desired product had reduced slightly to 50% conversion and the *dr* had also reduced to 70:30 (Table 18, entry 2). The reducing amount of product is likely to be due to a more competitive retro-addition reaction as the *β*-nitroamine product **292** is less stable with a quaternary centre. By reducing the reaction temperature to -20 °C better conversion and diastereoselectivity could be obtained with approximately 76% of imine **291** converted to desired product **292** with a *dr* of 95:5 after 20 h (Table 18, entry 4). It appears at this point there exists a dynamic equilibrium between the forward and reverse reaction as the conversion remained constant over the next 4 h (Table 18, entry 5).

Table 18. Reductive nitro-Mannich reaction with ketimines

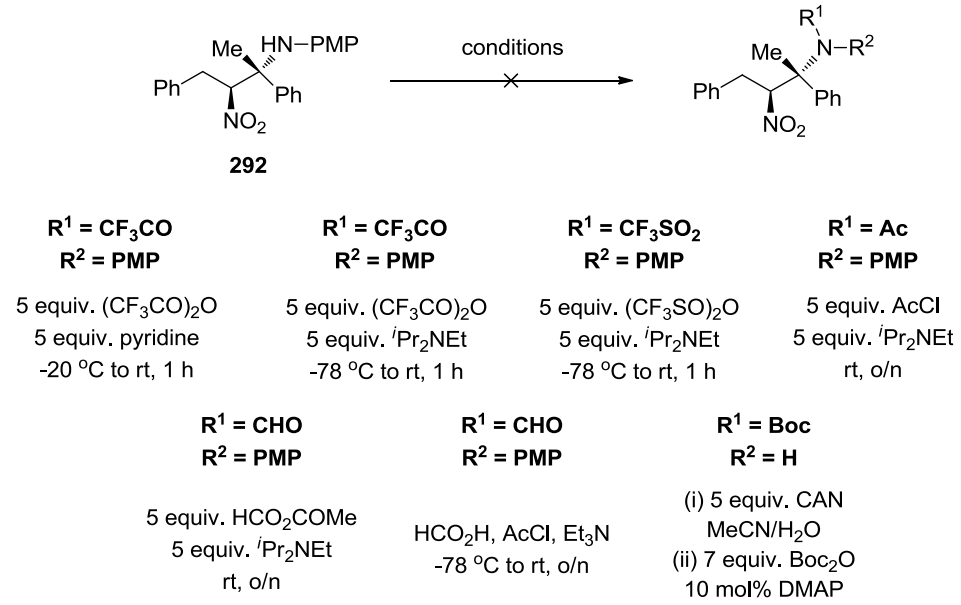


2.0 equivs. **84a** **291** **292**

Entry	Temp (^{o}C)	Time (h)	%. Conv[a]	*dr*[b]
1	rt	1	60	75:25
2	rt	2	50	70:30
3	-20	16	68	95:5
4	-20	20	76	95:5
5	-20	24	76	95:5

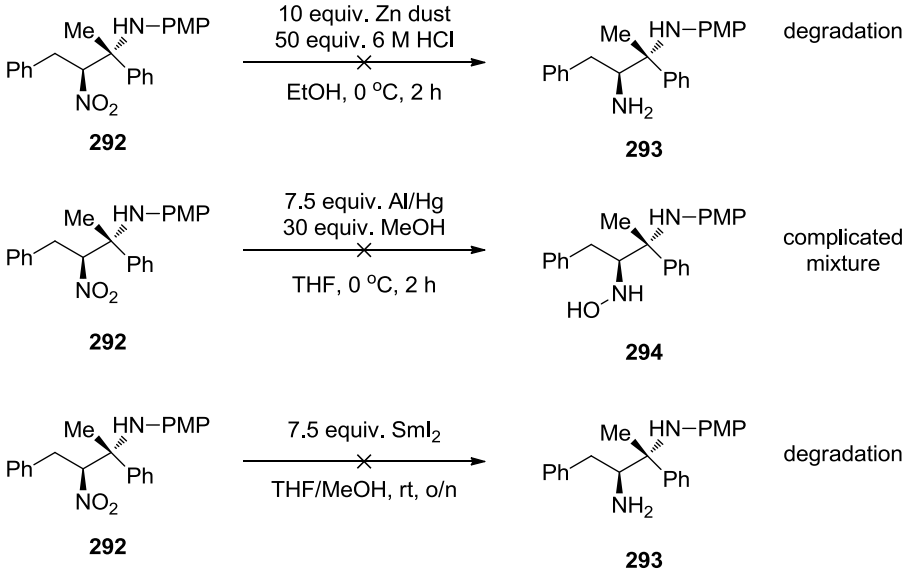
[a] % Conv. to **292** by ^{1}H NMR. [b] *dr* of crude **292** calculated from ^{1}H NMR.

The *β*-nitroamine product **292** is tentatively assigned as *anti* since the kinetic product from nitro-Mannich reactions is typically the *anti* diastereomer. It is assumed that the absolute stereochemistry is 2*R*,3*S* as shown based on the previous work with aldimines (see section 2.2.5). As with the reductive nitro-Mannich reaction with aldimines, *β*-nitroamine product **292** was unstable to chromatography. Unfortunately, **292** could not be protected as a trifluoroacetamide using the standard conditions (Scheme 112) meaning that the level of enantiopurity could not be determined. In addition to trifluoroacetamide protection a number of other strategies were also attempted but were unsuccessful including triflate protection; acetate protection, *via* ketene formation; formylation using acetic formic anhydride; and attempted removal of the PMP group using ceric ammonium nitrate (CAN), followed by Boc protection. Instead only degradation of *β*-nitroamine **292** was observed (Scheme 112).



Scheme 112. Attempted protection of *β*-nitroamine **292**

After the failed attempts to protect **292**, an *in situ* reduction was attempted (Scheme 113). Unfortunately, once more no desired reduced product was isolated with either a complex mixture of products obtained or degradation of *β*-nitroamine **292** by retro-addition observed. One of the problems with the reduction methods is that they are all in different solvents to the reaction solvent choice for the reductive nitro-Mannich reaction (toluene).



Scheme 113. Attempted reduction of *β*-nitroamine **292**

It could be imagined that when conducting a solvent swap, *β*-nitroamine **292** is already undergoing degradation. To check this, a small aliquot was removed from a

solution of **292** after a solvent swap from toluene to tetrahydrofuran. Indeed, significant degradation had occurred making it difficult to ascertain whether the reduction conditions had caused degradation in previous reactions. It may be possible to perform a reduction without altering the reaction solvent but due to time constraints such reactions have not been attempted.

2.2.8 Concluding paragraph

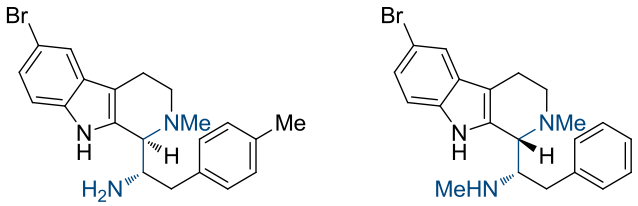
In this section, the development of an enantioselective tandem reductive nitro-Mannich reaction of nitroalkenes using thiourea organocatalysis has been described. This was achieved using Hantzsch ester **254** as the hydride source, *N*-PMP protected imines **30**, and thiourea **272** as a simple organocatalyst. The reaction formed the desired *β*-nitroamines which after protection as trifluoroacetamides **239** could be isolated in moderate to high yields (32-83% yield) excellent diastereoselectivities (typically >90:10 *dr*) and good to excellent enantioselectivity (73-99% *ee*) in the majority of cases. The reaction was uniformly diastereo- and enantioselective when the nitroalkene was altered however; the rate of reaction was greatly altered when using more electron rich nitroalkenes leading to lower yields due to competitive reduction of imine **30a**. Various heterocyclic, electron rich and electron deficient aromatic imines all gave excellent results but when using more sterically hindered *ortho*-tolyl or *ortho*-trifluoromethyl substituted imines lower stereoselectivity was observed (80:20 crude *dr*, 80-90% *ee*). Alkyl imines such as the ^{n}pentyl substituted imine **30i** were poorly enantioselective in the reaction however the cause of this is currently unknown. It is proposed that the high enantioselectivity of the reaction is the result of a cyclic transition state which is stabilised by multiple cooperative H-bonding interactions between the substrates and thiourea catalyst **272**, however this transition state is currently only speculative. The ability of the reaction to promote the reductive nitro-Mannich reaction with *α*-methyl-*β*-nitrostyrene **286** has also been investigated and the desired *β*-nitroamine bearing three contiguous stereocentres was isolated in a 32% yield as a single diastereomer (*syn,anti*) and in 84% *ee*. The reaction initially formed *syn,syn* diastereomer **287b** but over time converted to the *syn,anti* diastereomer **287a** which is believed to be the thermodynamic product. Some comparisons with this result and the results obtained in the similar conjugate addition/nitro-Mannich reactions of nitroalkenes with dialkyl

zincs were also drawn. Finally, the ability of thiourea **272** to promote the reaction with ketimine **291** was examined. Although, from ^{1}H NMR data, desired *β*-nitroamine **292**, bearing a quaternary centre, appears to have been synthesised it is too unstable to isolate and currently all attempts to protect or reduce **292** have failed.

2.3 Towards the total synthesis of Eudistomidin B

2.3.1 Introduction and retrosynthesis

Eudistomidin B is a member of a family of alkaloids and was first isolated in 1990 by Kobayashi and co-workers from the Okinawan marine tunicate *Eudistoma glaucus.*[143] It was found to display some interesting biological activities including potent cytotoxicity against murine leukaemia cells L1210 (3.4 μg/mL) and L5178Y (3.1 μg/mL). In addition Eudistomidin B also activated rabbit heart muscle actomyosin ATPase by 93% at $3x10^{-5}$ M. Eudistomidin B is comprised of a tetrahydo *β*-carboline with a bromine atom substituted in the 5-position. It also features a vicinal diamine and as such could potentially be accessed by a nitro-Mannich reaction.

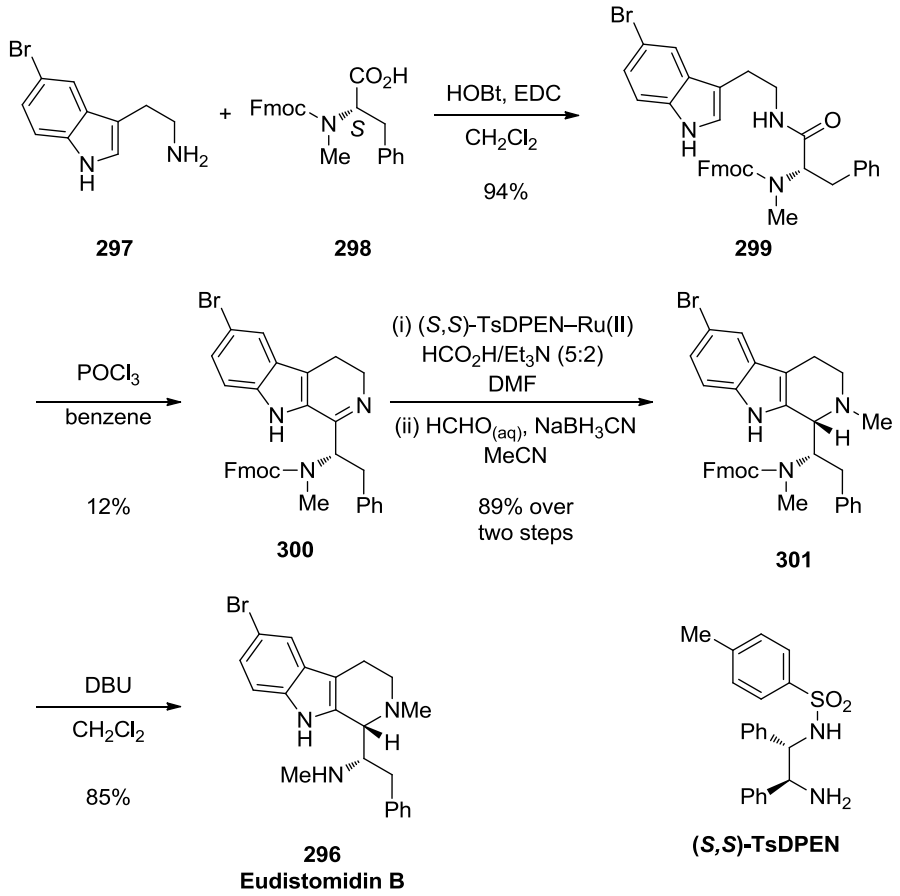


295
reported structure of
Eudistomidin B

296
revised structure of
Eudistomidin B

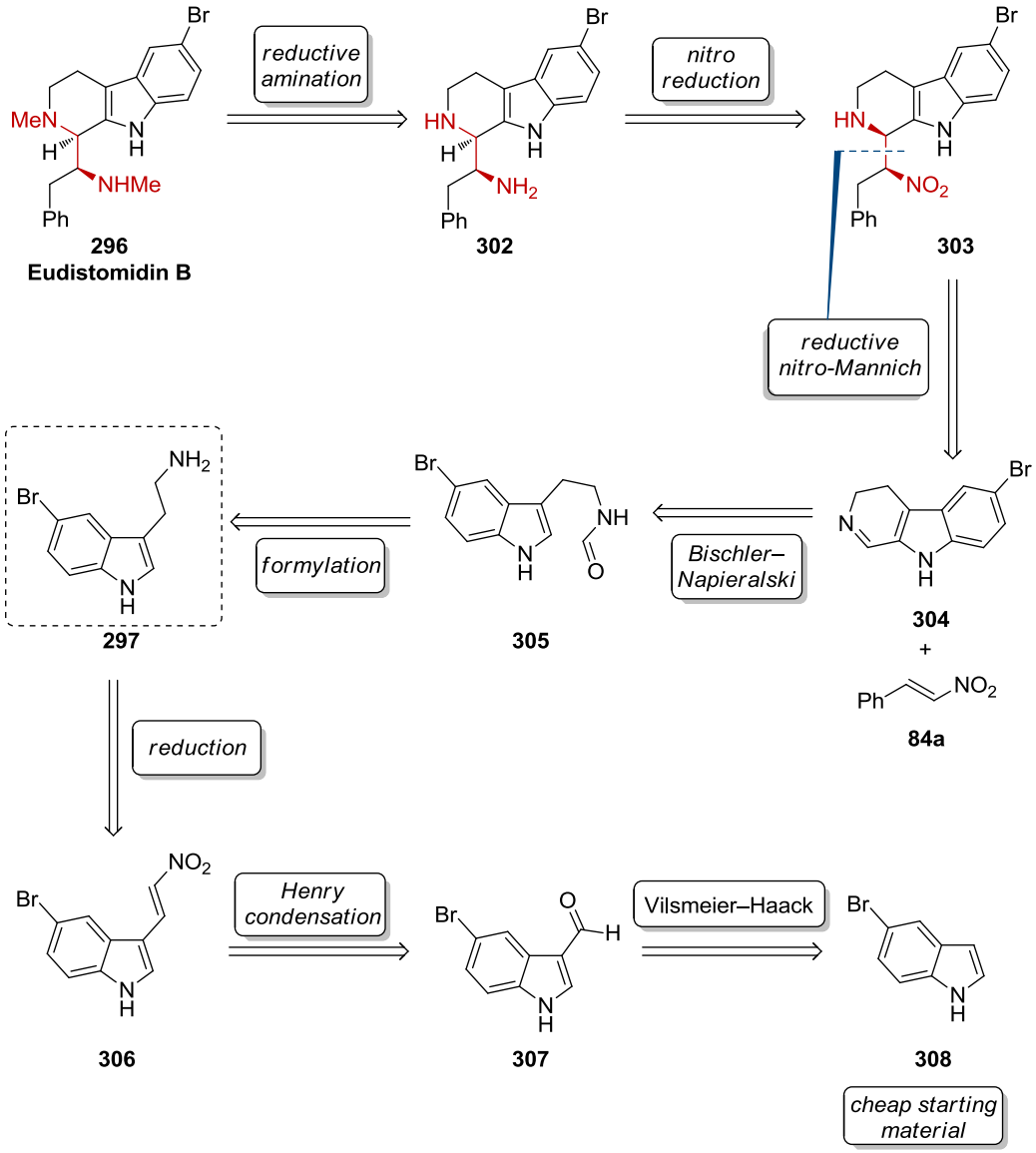
Figure 31. Original reported and revised structure of Eudistomidin B

The first enantioselective total synthesis of Eudistomidin B was reported in 2009 by Takayama with an overall yield of 0.12% over 20 steps but the NMR data of the natural and synthesised material contained several differences prompting the authors to question the proposed structure of Eudistomidin B.[144] In 2010, Kobayashi *et al.* proposed a new structure for Eudistomidin B (Figure 31) and completed the first total synthesis in an overall yield of 9% over 5 steps starting from chiral amino acid **298** and 5-bromotryptamine **297** (Scheme 114). In that synthesis, the only low yielding step was the Bischler-Napieralski reaction of **299** which gave ketimine **300** in 12% yield. Additionally, neither of the starting materials are particularly cheap.



Scheme 114. First total synthesis of Eudistomidin B

An alternative synthesis of Eudistomidin B could be to use a reductive nitro-Mannich reaction as proposed in scheme 115. Eudistomidin B could be accessed by mono-methylation of each of the amines of diamine **302**, which itself could be obtained from a reduction of *β*-nitroamine **303**. This *β*-nitroamine could be derived from a reductive nitro-Mannich reaction between imine **304** and *β*-nitrostyrene **84a**. Imine **304** should be easily formed by a Bischler-Napieralski reaction of formamide **305** with $POCl_3$, and formamide **305** could be simply synthesised from 5-bromotryptamine **297**. Using known chemistry from the literature 5-bromotryptamine **297** could be readily sourced from 5-bromoindole **308**.[145] But since 5-bromotryptamine **297** could be sourced commercially, the synthesis was started from this point.



Scheme 115. Retrosynthesis of Eudistomidin B

One observation that stands out amongst this synthetic scheme is that *β*-nitroamine **303** has a *syn* relationship. This is the opposite diastereoselectivity to what has been observed in the reductive nitro-Mannich reaction with *N*-PMP protected imines. However, there is a key difference between *N*-PMP protected imines and imine **304**. Whereas *N*-PMP imines exist in the *E* conformation, imine **304** is locked in the *Z* conformation. It is proposed that this should result in a *syn* selective reaction rather than an *anti* selective reaction, as when locked in a *Z* conformation the substituents should be forced into *pseudo* equatorial positions (Figure 32). If this transition state is correct then catalyst **272** based on natural *L*-valine should provide the product with the desired absolute chemistry.

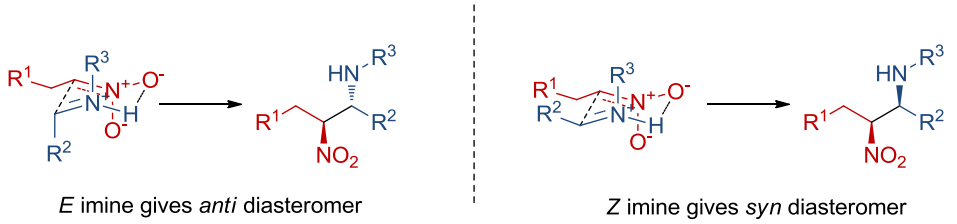
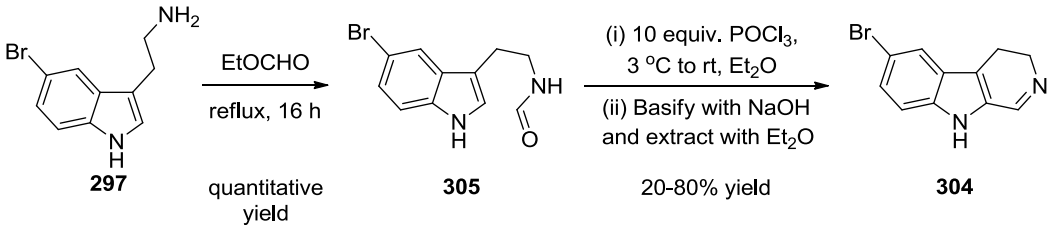


Figure 32. Nitro-Mannich reaction transition state for a *Z* imine

2.3.2 Forward synthesis route

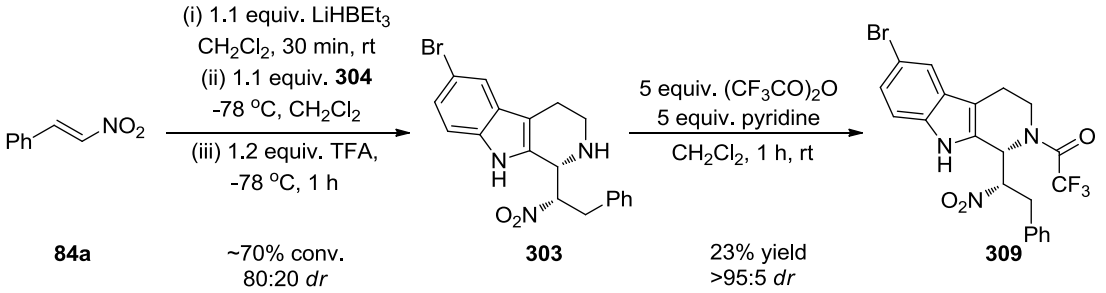
The first stage of the proposed synthesis was the formylation of 5-bromotryptamine **297** to give formamide **305**. This could be simply achieved by refluxing in ethylformate overnight to give formamide **305** in a quantitative yield. The second step was the synthesis of imine **304**. Although imine **304** is not known in the literature, its non-brominated analogue is and so the literature synthesis of this was followed.[146] The literature procedure described addition of the formamide as a solid in one portion to a solution of neat $POCl_3$ at 3 ^oC. As this procedure reported an exotherm of 60 ^oC it was decided to add formamide **305** portionwise. After 2 h at 3 ^oC imine **304** was formed and could be filtered to give the acid salt of **304** in excellent purity in 85% yield. However, upon attempting to isolate the free base of imine **304** variable yields were obtained (20-80%).



Scheme 116. Synthesis of nitro-Mannich reaction pre-cursor

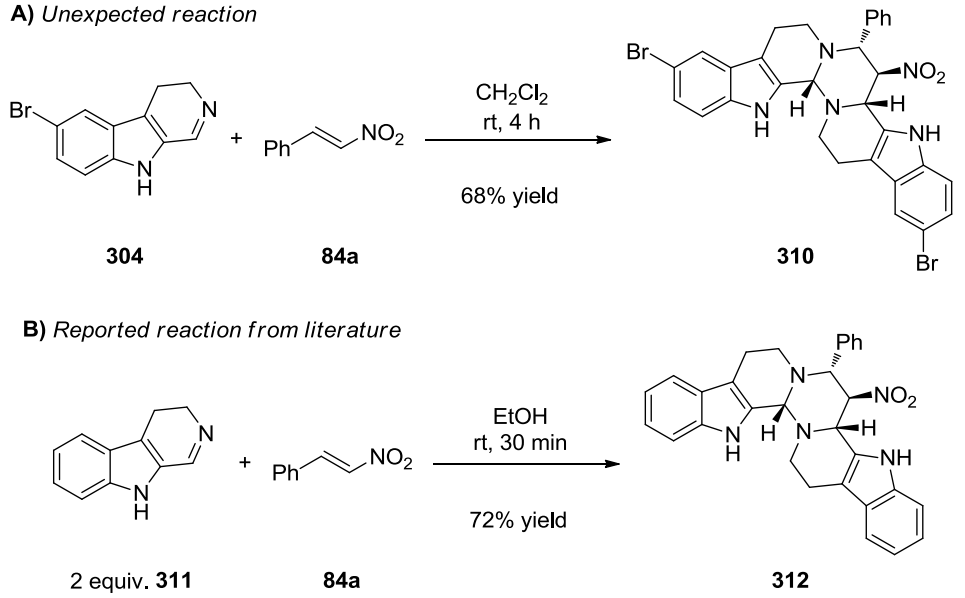
As this reaction was only attempted a few times the cause of this variability has yet to be discovered. It was also found that imine **304** was quite unstable and could not be stored for more than 3 days at -20 ^oC before significant degradation had occurred. The acid salt of imine **304** was slightly more stable but also underwent degradation after one week at -20 ^oC. With imine **304** in hand the reductive nitro-Mannich reaction could be attempted. Initially the racemic reaction using Superhydride^{TM} was performed and pleasingly, after addition of trifluoroacetic acid desired β-nitroamine **303** was observed in a 80:20 *dr* and with 70% conversion. Crucially the coupling constants, of the protons in the α-position to the amino and nitro group, of the major

(J = 8.3 Hz) and minor (J = 4.9 Hz) diastereomers seem to suggest preferential formation of the *syn* diastereomer. Trifluoroacetamide protection was also successful to give **309** in a 23% yield. However, the product was slightly unstable and degraded before full data could be collected.



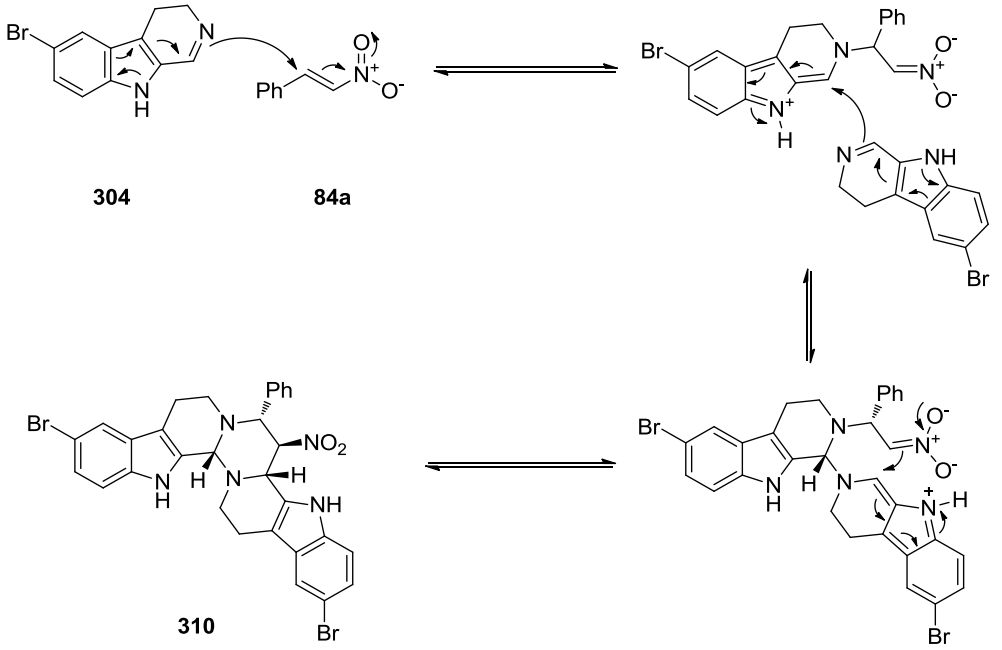
Scheme 117. Racemic reductive nitro-Mannich reaction with imine **304**

Despite this, it was felt that an alternative protection strategy or rapid reduction could overcome this stability issue so examination of the asymmetric variant was performed. The reaction with thiourea catalyst **272** however, failed to give the desired product instead an unknown compound was formed. As imine **304** was insoluble in toluene it was thought that this may have prevented the reaction from succeeding and as such it was then attempted to perform the reaction in dichloromethane. Imine **304** was also found to be insoluble in dichloromethane but the reaction was continued regardless.



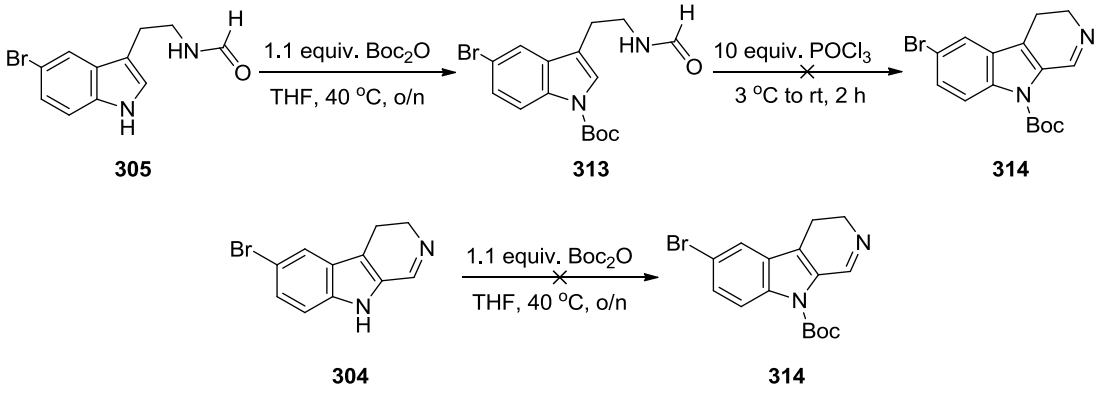
Scheme 118. A) Unexpected reaction with imine **304** and B) Literature reaction

It was observed that upon addition of nitroalkene **84a** to a suspension of imine **304** the reaction became homogenous suggesting a possible reaction. This reaction was then left to age for 4 h upon which precipitation of the unknown product occurred and was isolated in a 68% yield based upon limiting reagent *β*-nitrostyrene **84a** reacting with imine **304** in a 1:2 molar ratio.



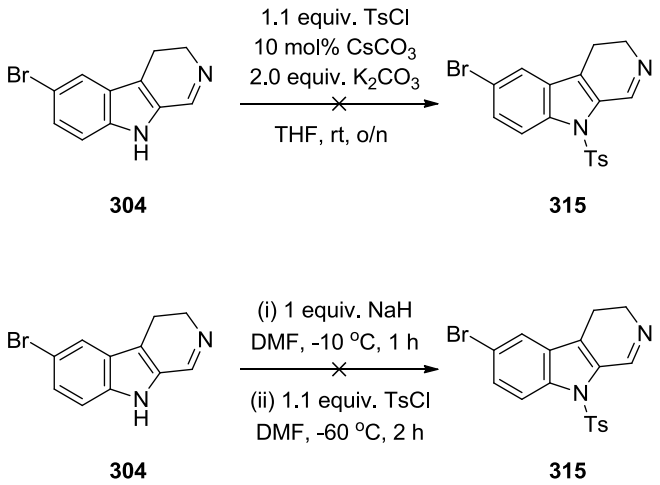
Scheme 119. Proposed mechanism of formation of **310**

From examining the ^{1}H NMR and mass spectra it was proposed that the unknown product formed was **310** (Scheme 118, A). A literature search revealed a similar structure has been formed by the same reaction of an imine **311** and nitroalkene **84a** previously by simply stirring in ethanol to give **312** in an 85% yield, although no data was given for this compound (Scheme 118, B).[147] The proposed mechanism for the formation of **310** is shown in scheme 119.



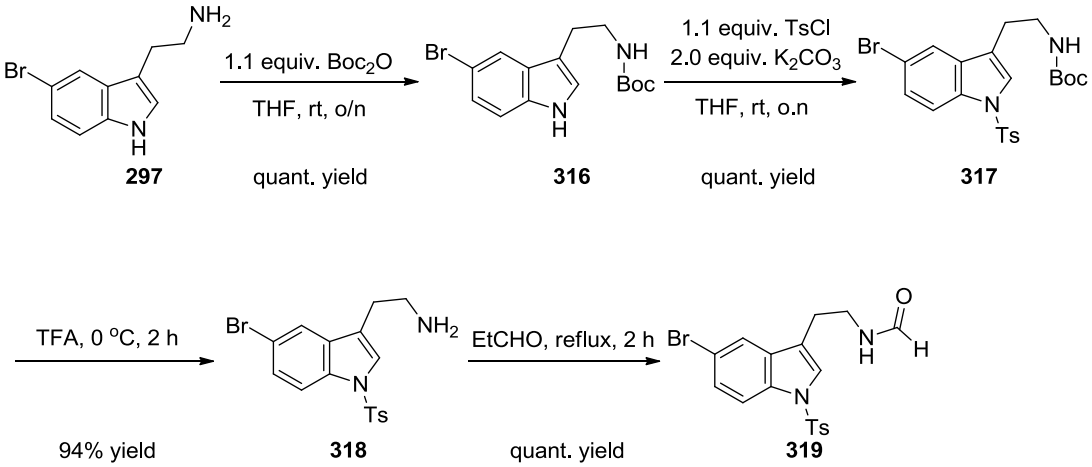
Scheme 120. Attempts to synthesise *N*-Boc protected imine **314**

It was assumed that the cause of this reaction was the use of extremely electron rich imine **304**. It was hoped that by placing an electron withdrawing protecting group on the indole ring this undesired reaction could be suppressed. Initially, it was attempted to form *N*-Boc protected imine **314**. Formylated tryptamine **305** could be selectively protected by gently heating with di-*tert*-butyl carbonate in tetrahydrofuran to form *N*-Boc protected product **313**. Unfortunately, attempts to form imine **314** failed instead forming imine **304** after unsurprisingly Boc deprotection occurred due to the acidic conditions. Attempts to *N*-Boc protect this imine also failed and only degradation was observed (Scheme 120).



Scheme 121. Attempted tosylation of imine **304**

It was next attempted to form *N*-tosylated imine **315**. Initial efforts to achieve this directly from imine **304** failed despite literature precedent that described the same reactions on an un-brominated analogue (Scheme 121).[148] After this failed It was attempted to first synthesise cyclisation precursor **319**.



Scheme 122. Synthesis of tosylated formyl tryptamine **319**

This could be achieved, albeit in a circuitous fashion from 5-bromotryptamine (Scheme 122). First, 5-bromotryptamine **297** was Boc protected to give **316** which was then selectively tosylated to give orthogonally protected **317**. The Boc group could then be removed under acidic conditions and formylated in ethyl formate to give **319** in a 94% yield over 4 steps. With formamide **319** in hand the Bischler-Napieralski reaction was attempted (Table 19).

Table 19. Examination of various reaction conditions for Bischler-Napieralski reaction

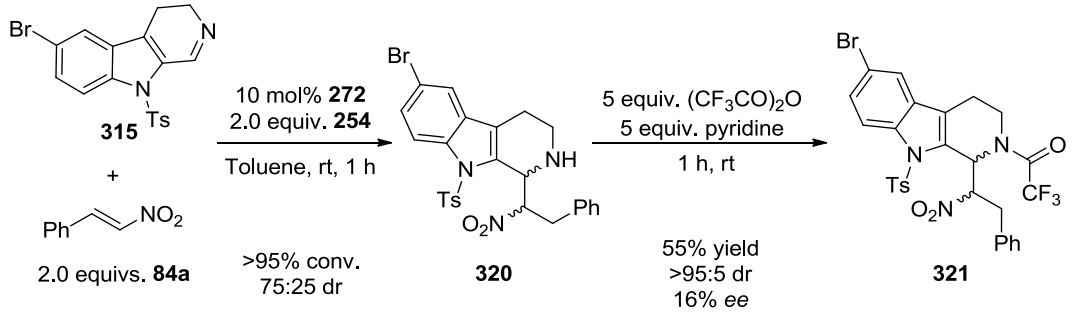
319 **315**

Entry	Solvent	Reaction conditions	% Yield[a] of 315
1	neat	10 equiv. $POCl_3$, rt, 16 h	0
2	toluene	10 equiv. $POCl_3$, 110 ^oC, 16 h	0
3	acetonitrile	10 equiv. $POCl_3$, 82 ^oC, 16 h	15
4	propionitrile	10 equiv. $POCl_3$, 98 ^oC, 16 h	7
5	degassed acetonitrile	10 equiv. $POCl_3$, 82 ^oC, 16 h	15-45
6	dichloromethane	1.2 equiv. 2-Cl-pyridine, 1.1 equiv. Tf_2O, -78 ^oC 5 min, 140 ^oC 30 min MW	0

Reactions performed on 50 mg scale. [a] isolated yield of **315**.

Attempts to perform the desired reaction in neat $POCl_3$ failed to give the desired reaction (Table 19, entry 1) as did the reaction in toluene at reflux (Table 19, entry 2). Some desired product was observed when acetonitrile was used as solvent and **315** was isolated in 15% yield (Table 19, entry 3). Using higher boiling propionitrile as the solvent however, gave a lower reaction yield of 7% (Table 19, entry 4). Although its identity could not be confirmed it was suspected that one of the by-products from the reaction was from oxidation of **315** to form the fully aromatised *β*-carboline ring. For this reason it was attempted to degas the acetonitrile and pleasingly desired product **315** was obtained in a moderate 45% yield (Table 19, entry 5). However, upon increasing the scale of the reaction to 100 mg only a 15% yield was obtained.

Unfortunately, due to time constraints the cause of this variability in yield could not be determined. Finally, the reaction was attempted using the conditions developed by Movassaghi *et al.* but no desired product was observed (Table 19, entry 6).[149]



Scheme 123. Asymmetric reductive nitro-Mannich reaction of imine **315**

With a small amount of *N*-tosylated imine **315** in hand, the asymmetric reductive nitro-Mannich reaction was attempted at room temperature using thiourea organocatalyst **272** (Scheme 123). Unlike with unprotected imine **304** the desired reductive nitro-Mannich reaction proceeded in good conversion (>95%) with a *dr* of 75:25. Unfortunately, the coupling constants of both diastereomers differed substantially from the expected values and as such it was not possible to identify whether the *syn* or *anti* diastereomer was formed. Pleasingly, *β*-nitroamine **320** could be protected as trifluoroacetamide **321** and the major diastereomer was isolated in a 55% yield. Regrettably, the product was only obtained in 16% *ee*. Performing the reaction at lower temperature (-20 ^{o}C) over 20 h did improve the enantioselectivity forming **321** in 48% *ee*, a similar level of diastereoselectivity, and in 33% yield. The difference in yield is thought to originate from experimental error due to the small scale the reactions are performed on rather than a difference in the reactivity at these temperatures. The increase in the enantioselectivity to 48% *ee* does suggest that the reaction could be optimised. The cause of the poor enantioselectivity compared to *N*-PMP imines is currently unknown but it is suspected that imine **315** is likely to have a different basicity to *N*-PMP imines **30** and hence may not bind to the catalyst as strongly. Another possible cause could be that the nitro-Mannich reaction does not proceed *via* a cyclic transition state. The coupling constants of *β*-nitroamine **320** are not indicative of a H-bonded cyclic conformation so it is plausible that a cyclic transition state does not occur as well.

Chapter 3. Conclusions and future studies

3.1 Conclusions

This doctoral thesis has successfully developed both a racemic and an asymmetric reductive nitro-Mannich reaction. The racemic variant was a continuation of previous work established in the group and it was found that the limitations of this research, namely an inability for the reaction to proceed with *β*-nitrostyrenes, could be overcome by using a stronger Brønsted acid (trifluoroacetic acid) and an alternative imine (*N*-PMP protected). With these changes a variety of *β*-nitroamines could be formed with conversion (>90%) and high diastereoselectivities (75:25 to >95:5 *dr*) by the one-pot Superhydride^{TM} reduction/nitro-Mannich sequence of nitroalkenes. It was also discovered that when using electron rich aromatic imines the diastereoselectivity of the reaction was poor. This problem was overcome by switching the solvent to a non-coordinating solvent such as dichloromethane. The *β*-nitroamines were protected by reaction with trifluoroacetic anhydride and pyridine, due to their instability towards purification, enabling isolation of the products as trifluoroacetamides in good to excellent yields (58-87%) and diastereoselectivity (>90:10 *dr*).

The enantioselective reductive nitro-Mannich reaction of nitroalkenes was achieved using thiourea organocatalysis. It was discovered that the desired reaction could be promoted in tandem using a Hantzsch ester as the hydride source, thiourea catalyst and *N*-PMP protected imine. After a careful catalyst screen, it was discovered that a very simple and economic catalyst could promote the reaction with exquisite levels of stereocontrol after one day at -20 ^{o}C. The reaction was then examined with a variety of different substrates and was found to work well in almost all examples. Once more, after protection as trifluoroacetamides, the resultant products could be isolated in moderate to excellent yields (32-84%), high diastereoselectivity (>90:10 *dr*) and good to excellent enantioselectivity (73-99% *ee*). Observations from these experiments have led to the proposal that the reduction is the rate determining step of the reaction and a H-bond stabilised six-membered transition state has been proposed as the enantiodetermining step. Additionally, a preliminary investigation into the ability of the catalyst to promote a reductive nitro-Mannich reaction using

α-methyl-β-nitrostyrene was examined to give the desired product containing three contiguous stereocentres as a single diastereomer in low yield (32%) and in 85% *ee*. The potential of the thiourea to catalyse a reductive nitro-Mannich reaction with ketimines was also explored. Although this reaction was successful, forming the desired product containing a quaternary centre in 95:5 *dr* and 80% conversion, it could not be isolated and the enantioselectivity was not calculated. These preliminary experiments should pave the wave for further studies in this area.

The final research of the thesis focussed on progress towards the synthesis of 1,2-diamine containing natural product Eudistomidin B, using a nitro-Mannich reaction as the key step. Using an unprotected *N*-*H*-indole containing pre-cursor an unexpected by-product was formed instead of the nitro-Mannich product. However it was later discovered that the desired tandem reductive nitro-Mannich would succeed when using a *N*-tosyl protected analogue to form the desired product in a 33% yield and 48% *ee* as a single diastereomer after purification. The synthesis was halted at this point due to time constraints but significant optimisation will be required to make this a viable route to Eudistomidin B.

3.2 Future studies

3.2.1 Asymmetric reductive nitro-Mannich reaction

Although, the reaction using simple catalyst **272** generally formed the desired products with excellent stereoselectivity and in good yields there were some limitations with the reaction. In particular, the reaction yield was poor when using more electron rich nitroalkenes due to a combination of a slow rate of reduction and competitive reduction of the *N*-PMP protected imine. To overcome these problems a more reactive hydride source may be required as simply increasing the reactivity of the catalyst is likely to result in an increased amount of the retro-nitro-Mannich reaction. A hydride source with only one electron withdrawing group should achieve this as You's group have shown such dihydropyridines are typically stronger hydride donors.[150]

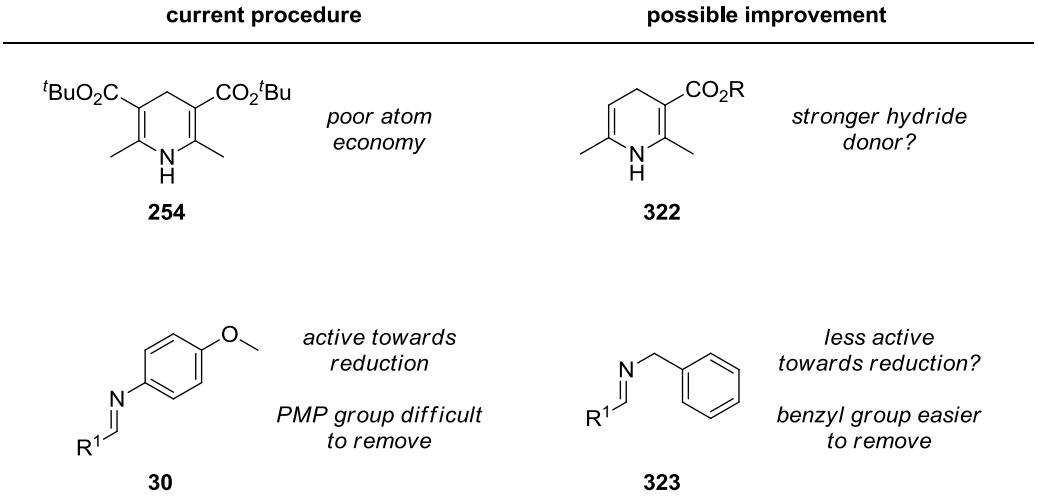
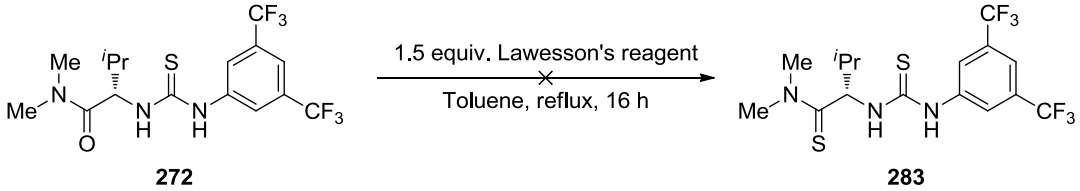


Figure 33. Possible improvements to enantioselective reductive nitro-Mannich reaction

This could also eventually lead to catalytic use of a dihydropyridine,[151] which would be valuable as Hantzsch ester **254** is not an atom economical reagent. Additionally a different imine-protecting group or a more selective thiourea organocatalyst would be required too as simply increasing the reactivity of the hydride source would not prevent competitive reduction of the imine. An alternative protecting group such as benzyl should result in an imine less active towards reduction as well as being easier to remove in subsequent synthesis steps. Another limitation of the reaction is the

poor reactivity with alkyl substituted imines. This is a difficult problem to fix as the majority of alkyl substituted imines exist in both the imine and enamine form and as such can either undergo oligomerisation, as in the case of *N*-PMP protected imines, or remain unreactive to nucleophilic attack by existing solely in the enamine form. A possible solution is to form the imine *in situ* so that only a small concentration of imine exists at any one point. Such a method has been previously utilised by Palomo *et al.* with a variety of *N*-Boc protected imines (see section 1.1.5, Scheme 22). Whether such a method could be applied in the reductive nitro-Mannich reaction is unclear as *N*-Boc imines were previously shown to undergo reduction in these conditions (see section 2.2.1, Scheme 96). Unfortunately, such a method could not be employed with *N*-PMP imines as their rate of formation is too rapid.

In addition to improving the reaction, a detailed investigation into the mechanism of the reaction should be initiated. In section 2.2.5 the synthesis of alternative catalyst structures to probe the mechanism of the enantiodetermining step were touched upon. Another catalyst structure which should help to educate about the mechanism would be thioamide catalyst **283** whose synthesis was attempted using Lawesson's reagent directly from **272** (Scheme 124). This was only attempted once however, and appears straightforward enough. Synthesis of **283** could provide useful evidence as to whether a H-bond interaction exists between the iminium species and the (thio)amide moiety of the catalyst as this bond should be weaker with catalyst **283** and hence result in lower enantioselectivity. Although, methyl ester catalyst **282** has already been synthesised and suggests this interaction is not as important as first thought (see section 2.2.5, Table 14), for the sake of completeness and to provide further evidence synthesising thioamide catalyst **283** seems like a worthwhile pursuit.



272 **283**

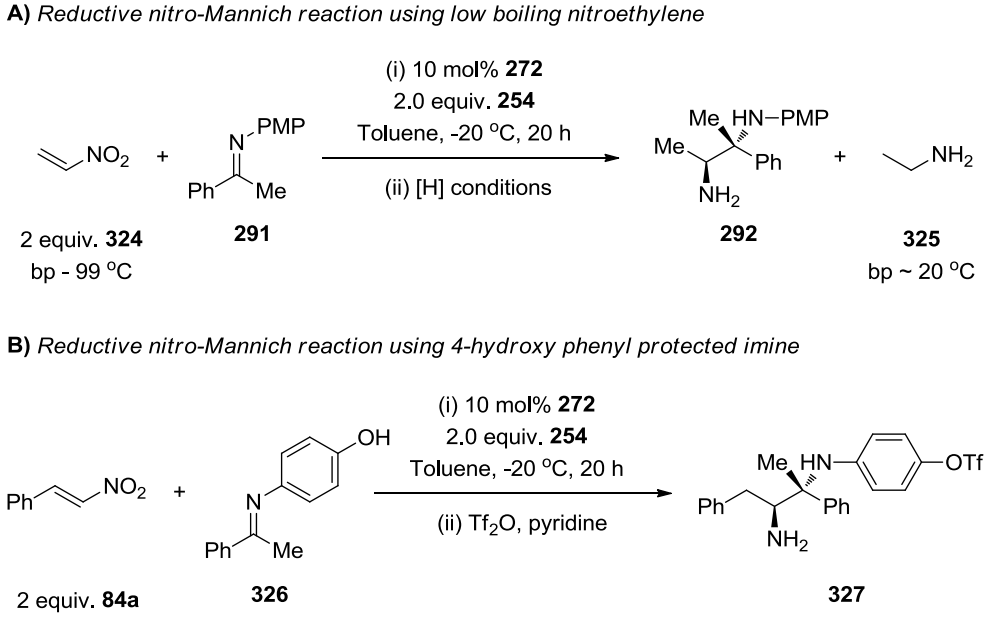
Scheme 124. Attempted synthesis of thioamide containing catalyst

Given the unexpected result with methyl ester catalyst **282** and the simplicity of catalyst **272** it seems sensible to examine the possibility that this nitro-Mannich reaction is catalysed by more than one thiourea unit. To examine this possibility, the order of the reaction with respect to the catalyst would need to be determined.

However, this would only provide information about the rate determining step, which is believed to be the reduction step, and would not necessarily inform about the enantiodetermining step. Another, series of experiments could set out to uncover relationships between the enantiopurity of the catalyst and the enantiopurity of the resultant product. Any deviations from linearity would suggest that the catalyst is a heterodimeric species in the enantiodetermining step and may help to explain the high levels of enantioselectivity.[152] Computational studies may offer the best solution to determining the mechanism of the enantio-determining step and there have been several theoretical studies performed on thiourea catalysts, including some with similar structures to the catalyst used in the reductive nitro-Mannich reaction.[84]

3.2.2 Asymmetric reductive nitro-Mannich reaction of ketimines

The enantioselective reductive nitro-Mannich reaction with ketimines has shown some promise as the desired *β*-nitroamine is formed but cannot be isolated. *In situ* reduction may offer a solution but currently, either complex mixtures or degradation products have been isolated. One of the problems of the reaction is due to the large number of components in the reaction complicating the spectra. An idea that could make identification of products easier could be to use nitroethylene **324** as the nitroalkene rather than *β*-nitrostyrene (Scheme 125, A).

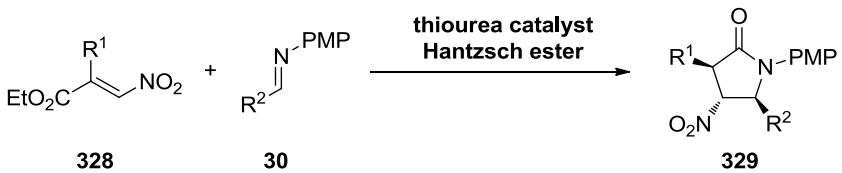


Scheme 125. Possible solutions to the instability of *β*-nitroamines with a quaternary centre

The unreacted nitroethylene or its reduction products could then be removed from the reaction under vacuum as both are low boiling (nitroethylene bp ~ 99 ^{o}C, ethylamine bp ~ 20 ^{o}C). Nitroethylene may also be more reactive than *β*-nitrostyrene enabling complete conversion of imine **291** to occur before the retro-addition is competitive. Another possible solution to the poor stability could be to use a hydroxy imine such as **326**. This could then be protected after the nitro-Mannich reaction to form a more stable *β*-nitroamine such as **327** which may be stable to purification (Scheme 125, B). However, ketimine **326** may be very insoluble in a solvent such as toluene so the feasibility of such a reaction is unknown.

3.2.3 Reductive nitro-Mannich reaction to form three stereocentres

The preliminary result into the potential to build *β*-nitroamines with three contiguous stereocentres using the reductive nitro-Mannich reaction showed good promise forming the desired product in a 32% yield, as a single diastereomer and in 84% *ee*. The reaction is limited by similar problems to the reductive nitro-Mannich reactions with electron rich nitroalkenes in that the rate of reaction is slow and that competitive reduction of *N*-PMP imine **291** occurs. A more selective reduction of nitroalkenes is required and further catalyst screening would need to be performed to achieve this. Another reaction that could be examined which should result in a more selective reduction of the nitroalkene over the imine would be the reductive nitro-Mannich reaction of substituted nitroacrylates such as **328**. These should then also cyclise to form enantiomerically enriched pyrrolidinones (Scheme 126). The Anderson group have previously synthesised such compounds using the conjugate addition/nitro-Mannich reaction with diethyl zinc,[55] and List's group have performed asymmetric reductions of nitroacrylates,[103] so there is good literature precedence for such a reaction.

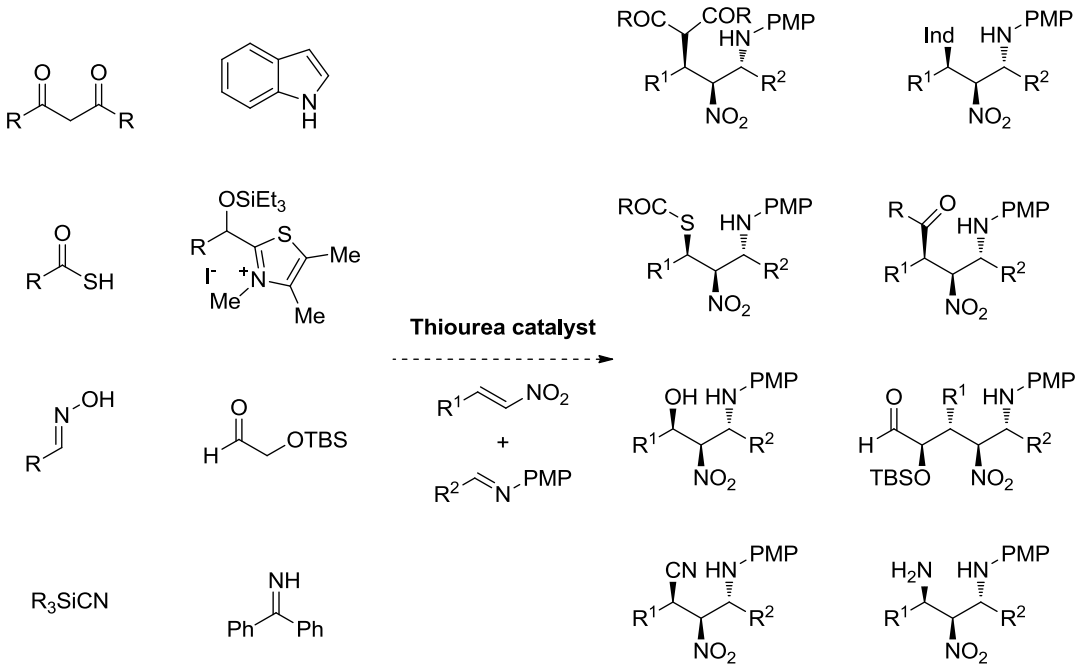


328 **30** **329**

Scheme 126. Reductive nitro-Mannich reaction of nitroacrylates

3.2.4 Tandem nitro-Mannich reactions with different nucleophiles

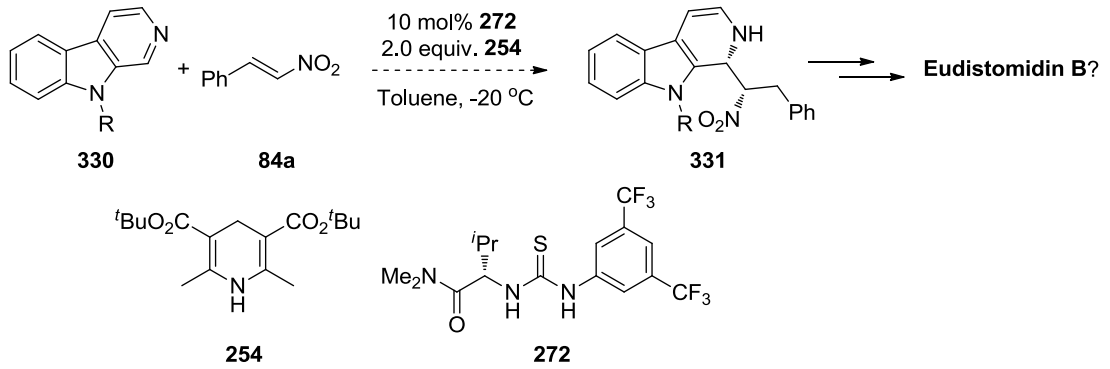
As was discussed in the introduction (see section 1.3.4) thiourea organocatalysis has been used to promote the addition of a variety of nucleophiles to nitroalkenes. It would be of great interest to investigate the possibility of performing some of these additions in tandem with a nitro-Mannich reaction. Scheme 127 shows some of the possible transformations.



Scheme 127. Other possible thiourea catalysed tandem nitro-Mannich reactions

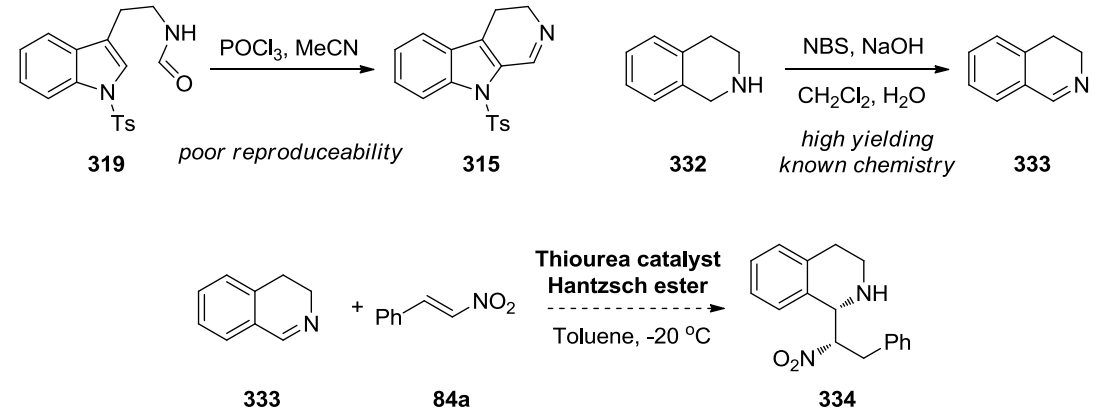
3.2.5 Total synthesis of Eudistomidin B

The total synthesis of Eudistomidin B was halted after poor enantioselectivity for the nitro-Mannich reaction was observed. It is thought that the cause of this may be the basicity of imine **315** which is likely to be different to *N*-PMP protected imines **30** used in the earlier research. It is likely that further catalyst screening will be required to overcome this low enantioselectivity. One alternative may be to attempt the reductive nitro-Mannich reaction on *β*-carboline **330** as this should have similar basicity to the *N*-PMP imines. However, as to whether the nitro-Mannich reaction would be able to break the aromaticity of such a system is unclear.



Scheme 128. Use of a *β*-carboline in the reductive nitro-Mannich reaction

If a catalyst screen was to be performed, due to the poor reproducibility of the Bischler-Napieralski reaction to synthesise imine **315** it may be better to develop the initial reductive nitro-Mannich methodology on 3,4-dihydroisoquinolines **333** as these should hopefully react in a similar manner but can be synthesised much more readily (Scheme 129).[153] Such a reaction would also be of use to the synthetic community as currently, no diastereoselective nitro-Mannich reactions to form *β*-nitroamines such as **334** are known. Additionally, only a single enantioselective nitro-Mannich reaction of 3,4-dihydroisoquinolines has been reported.[154]



Scheme 129. Reductive nitro-Mannich reaction of 3,4-dihydroisoquinolines

Chapter 4. Experimental

4.1 General experimental

4.1.1 General experimental details

Unless specified otherwise for all non-aqueous chemistry, glassware was flame-dried under an inert (N_2 or Ar) atmosphere. Cryogenic conditions (-78 ^oC) were achieved using solid carbon dioxide/acetone baths. Temperatures of -100 ^oC were achieved using a liquid N_2/toluene bath and reaction temperatures of -20 ^oC were achieved using a NESLAB CB-80 Cryobath. Temperatures of 0 ^oC were obtained by means of an ice bath. Room temperature indicates temperatures in the range of 20-25 ^oC.

For the purposes of thin layer chromatography (tlc), Merck silica-aluminium plates were used, with *uv* light (254 nm) and potassium permanganate used for visualisation. For column chromatography, Apollo Scientific ZEOprep 60 or Merck Geduran® Si 60 silica gel was used. Removal of solvents (*in vacuo*) was achieved using a Vacuubrand diaphragm pump or house vacuum and Büchi rotary evaporators.

All NMR data was collected using a Bruker AMX 300 MHz, Bruker AVANCE III 400 MHz, Bruker AVANCE 500 MHz or Bruker AVANCE III 600 MHz. Data was manipulated directly using Bruker XwinNMR (version 2.6) or TopSpin (version 2.1). Reference values for residual solvents were taken as $\delta = 7.27$ ($CDCl_3$) and 2.51 ppm (DMSO-*d*6) for ^1H NMR; $\delta = 77.16$ ppm ($CDCl_3$) for ^{13}C NMR. Multiplicities for coupled signals were denoted as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad, apt. = apparent and dd = double doublet *etc.* Coupling constants (*J*) are given in Hz and are uncorrected. Where appropriate, COSY, DEPT, HMBC, HMQC and NOE experiments were carried out to aid assignment. Mass spectroscopy data was collected on a Thermo Finnigan Mat900xp **(**EI/CI) VG-70se (FAB) and Waters LCT Premier XE (ES) instruments. Infrared data was collected using a Perkin-Elmer 1600 FTIR machine as a thin film unless otherwise stated. Elemental analysis was performed on an Exeter Analytical Inc. EA440 horizontal load analyser. Melting points are uncorrected and were recorded on a Stuart Scientific SMP3 system. Optical rotations were obtained using a Jasco DIP370 digital polarimeter and are reported in deg cm^2 g^{-1}. Chiral HPLC was performed using either a Chiralcel AD 25 cm analytical column or an OD-H 15 cm analytical column.

Samples were dissolved in solutions of MeCN/^{i}PrOH/^{n}hexane (5:15:80) to concentrations of 2.5 mg/mL.

4.1.2 Purification of reagents

All solvents and reagents were used as supplied or purified using standard techniques,[155] unless alternatively specified herein. All solutions of organo-lithium reagents were standardised with diphenyl acetic acid. Activation of molecular sieves was achieved by flame-drying under high vacuum.

Cyclohexane carboxaldehyde was distilled from calcium hydride powder under reduced pressure and stored in a darkened refrigerator.

(R,R)-1,2-Diaminocyclohexane mono-(+)-tartrate was resolved from (±)-*trans*-1,2-diaminocyclohexane using *L*-(+)-tartaric acid according to literature procedure.[156]

Dichloromethane was obtained from a solvent tower, where degassed dichloromethane was passed through two columns of alumina and a 7 micron filter under 4 bar pressure.

Diethyl ether was obtained from a solvent tower, where degassed diethyl ether was passed through two columns of alumina and a 7 micron filter under 4 bar pressure.

^{n}Hexanal was distilled from calcium hydride powder and stored in a darkened refrigerator.

β-Nitrostyrene was recrystallised from diethyl ether and stored in a darkened freezer.

(E)-2-(2-Nitrovinyl)pyridine was stored in a darkened refrigerator and passed through a short column of silica prior to use.

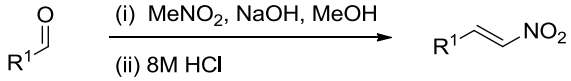
2-Pyridine carboxaldehyde was distilled and stored in a darkened refrigerator.

Tetrahydrofuran was obtained from a solvent tower, where degassed tetrahydrofuran was passed through two columns of alumina and a 7 micron filter under 4 bar pressure.

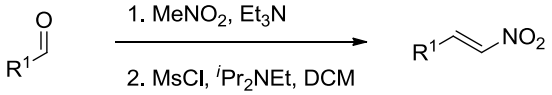
Toluene was obtained from a solvent tower, where degassed toluene was passed through two columns of alumina and a 7 micron filter under 4 bar pressure.

4.2 Synthetic procedures

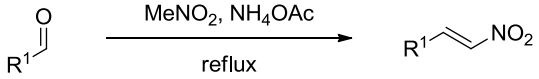
4.2.1 Procedures for preparation of nitroalkenes



General procedure A: 1.0 M NaOH (2.5 mL per mmol) was added to a solution of $MeNO_2$ (2.5 equiv.) and carbonyl compound (limiting reagent) in MeOH (7.5 mL per mmol) at 0 °C (*CAUTION: EXOTHERM!*). After a 10 min stir, ice water (2.0 mL per mmol) was added and the mixture charged to a dropping funnel. The mixture was then added dropwise to 8.0 M HCl (2.0 mL per mmol) over 30 min at 0 °C (*CAUTION: EXOTHERM!*). The reaction was stirred for 1 h after which time the product was collected by filtration if precipitation had occurred. If precipitation did not occur, the mixture was extracted with CH_2Cl_2 (3 x 5.0 mL per mmol) and the combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo* to leave crude nitroalkene.

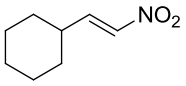


General procedure B: Carbonyl compound (limiting reagent), $MeNO_2$ (5.0 equiv.) and Et_3N (0.35 equiv.) were stirred overnight under N_2 at rt. Once reaction complete, as judged by tlc analysis, the excess $MeNO_2$ and Et_3N were removed *in vacuo*. Crude nitroalcohol was then dissolved in CH_2Cl_2 (10 mL per mmol) and cooled to 0 °C. To this solution was then added dropwise MsCl (1.2 equiv.) and the solution was stirred for 5 min. A solution of $^{i}Pr_2NEt$ (2.5 equiv.) in CH_2Cl_2 (2.0 mL per mmol) was then added *via* cannula over a period of 10 min. When the reaction was judged complete by tlc analysis (typically 1 h), it was returned to room temperature. The reaction was then washed with water (2 x 3.0 mL per mmol), 2.0 M HCl (2 x 3.0 mL per mmol), dried ($MgSO_4$) and concentrated *in vacuo* to leave crude nitroalkene.



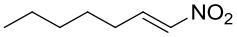
General procedure C: To a mixture of ammonium acetate (1.0 equiv.) and $MeNO_2$ (4.0 mL per mmol) was added carbonyl compound (limiting reagent) and the mixture was heated to reflux (105 ^{o}C). Once the reaction was judged complete by tlc analysis the reaction was cooled to rt and the excess solvent was removed *in vacuo*. The crude residue was then re-dissolved in CH_2Cl_2 (10.0 mL per mmol) and washed with sat. aq. $NaHCO_3$ 3.0 mL per mmol). The organic phase was then dried ($MgSO_4$) and the excess solvent removed *in vacuo* to leave crude nitroalkene.

(*E*)-(2-Nitrovinyl)cyclohexane 84b



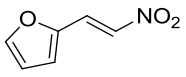
Prepared by General procedure B. Cyclohexanecarboxaldehyde (26.7 mmol) afforded after purification by column chromatography (8% Et_2O/pet. ether) **84b** (3.39 g, 21.8 mmol, 82% yield) as a pale yellow oil which solidified in the freezer; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.15-1.26 (3H, m, *Cy*), 1.26-1.37 (2H, m, *Cy*), 1.67-1.74 (1H, m, *Cy*), 1.74-1.85 (4H, m, *Cy*), 2.21-2.30 (1H, m, *Cy*), 6.93 (1H, dd, *J* = 13.4, 1.3, *H*C=C), 7.22 (1H, dd, *J* = 13.5, 7.2, *H*C=C). ^{1}H NMR data are consistent with literature data.[157]

(*E*)-1-Nitrohept-1-ene 84c



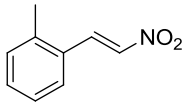
Prepared by General procedure B. ^{n}Hexanal (10.0 mmol) afforded after purification by column chromatography (2.5% Et_2O/pet. ether) **84c** (874 mg, 6.1 mmol, 61% yield) as a pale yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.0, C*H*$_3$), 1.26-1.38 (4H, m, (C*H*$_2$)$_2$), 1.47-1.56 (2H, m, ^{n}PrC*H*$_2$), 2.27 (2H, qd, *J* = 7.4, 1.5, ^{n}BuC*H*$_2$), 6.98 (1H, dt, *J* = 13.4, 1.5, ^{n}PnC*H*), 7.28 (1H, dt, *J* = 13.6, 7.5, C*H*NO_2). ^{1}H NMR data are consistent with literature data.[157]

(*E*)-2-(2-Nitrovinyl)furan 84d



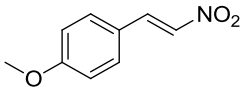
Prepared by General procedure A. 2-Furancarboxaldehyde (14.0 mmol) afforded **84d** (1.21 g, 8.7 mmol, 62% yield) as a yellow solid; mp 72-74 ^{o}C (Lit.[158] 74-75 ^{o}C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.58 (1H, dd, *J* = 3.5, 1.8, Ar*H*), 6.89 (1H, d, *J* = 3.4, Ar*H*), 7.52 (1H, d, *J* = 13.2, ArC*H*), 7.59 (1H, d, *J* = 1.3, Ar*H*), 7.77 (1H, d, *J* = 13.2, C*H*NO_2). ^{1}H NMR data are consistent with literature data.[158]

(*E*)-1-methyl-2-(2-nitrovinyl)benzene 84e



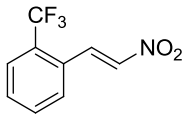
Prepared by General procedure A. *ortho*-Tolualdehyde (25.0 mmol) afforded crude **84e** which did not crystallise and was purified by column chromatography (5% EtOAc/pet. ether) to give **84e** (3.42 g, 21.0 mmol, 84% yield) as a yellow oil which solidified in the freezer; IR υ_{max} 3109 (C-H), 1630 (C=C), 1511 (N-O), 1337 (N-O), 1219, 963, 762 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.49 (3H, s, C*H*$_3$), 7.24-7.26 (1H, m, Ar*H*), 7.28 (1H, d, *J* = 8.3, Ar*H*), 7.36-7.41 (1H, m, Ar*H*), 7.49-7.54 (2H, m, Ar*H*, ArC*H*), 8.31 (1H, d, *J* = 13.6, C*H*NO_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.1 (*C*H_3), 126.9 (*C*H), 127.5 (*C*H), 129.0 (*C*), 131.5 (*C*H), 132.1 (*C*H), 136.9 (*C*H), 137.7 (*C*H), 139.4 (*C*); *m/z* (EI) 163 (36, M); HRMS $C_9H_9NO_2$ calcd. 163.0633, found 163.0628.

(*E*)-1-Methoxy-4-(2-nitrovinyl)benzene 84h



Prepared by General procedure A. 4-Methoxybenzaldehyde (22.0 mmol) afforded **84h** (2.09 g, 11.7 mmol, 53% yield) as a yellow solid; mp 79-81 ^{o}C (Lit.[159] 83-85 ^{o}C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.87 (3H, s, C*H*$_3$), 6.95 (2H, dm, *J* = 8.8. Ar*H*), 7.47-7.54 (3H, m, Ar*H*, ArC*H*), 7.98 (1H, d, *J* = 13.6, C*H*NO_2). ^{1}H NMR data are consistent with literature data.[159]

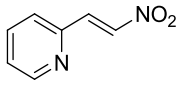
(*E*)-1-(2-nitrovinyl)-2-(trifluoromethyl)benzene 84i



Prepared by General procedure A. 2-(Trifluoromethyl)benzaldehyde (17.0 mmol) afforded **84i** (2.32 g, 10.7 mmol, 63% yield) as a yellow solid; mp 54-56 ^{o}C; IR υ_{max} 3108 (C-H), 1643 (C=C), 1516 (N-O), 1345 (N-O), 1311 (C-F), 1157, 1106 cm^{-1}; ^{1}H

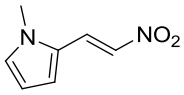
NMR (600 MHz, $CDCl_3$) δ 7.50 (1H, d, *J* = 13.6, *H*C=C), 7.58-7.69 (3H, m, Ar*H*, *H*C=C), 7.79 (1H, dd, *J* = 7.3, 0.9, Ar*H*), 8.38 (1H, dd, *J* = 13.6, 1.7, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 123.7 (1C, q, *J* = 274.0, *C*F_3), 127.0 (1C, q, *J* = 5.5, *Ar*H), 128.6 (C*H*), 128.7 (1C, m, *Ar*), 130.6 (1C, q, *J* = 30.8, *Ar*CF_3), 131.5 (*C*H), 132.6 (*C*H), 134.9 (1C, q, *J* = 2.2, *C*H), 139.9 (*C*H); *m/z* (EI) 217 (17, M), 170 (50, M–HNO_2); HRMS $C_9H_6F_3NO_2$ calcd. 217.0351, found 217.0343.

(*E*)-2-(2-Nitrovinyl)pyridine 84k



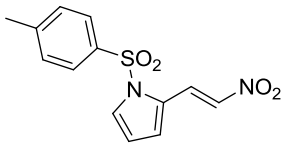
Prepared by General procedure B. *N*-Methyl-pyrrole-2-carboxaldehyde (15.0 mmol) afforded crude **84k** as a black solid which was purified by column chromatography (40% Et_2O/pet. ether) to give **84k** (900 mg, 6.0 mmol, 40% yield) as a yellow solid; mp 61-62 ^oC; IR υ_{max} 3121 (C-H), 3056 (C-H), 1638 (C=C), 1569, 1506 (N-O), 1345 (N-O), 963, 785 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (1H, dd, *J* = 7.6, 4.8, Ar*H*), 7.48 (1H, d, *J* = 7.7, Ar*H*), 7.79 (1H, td, *J* = 7.7, 1.9, Ar*H*), 7.92 (1H, d, *J* = 13.2, ArC*H*), 8.02 (1H, d, *J* = 13.2, C*H*NO_2), 8.69 (1H, d, *J* = 4.1, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 125.8 (*Ar*H), 126.5 (*Ar*H), 137.3 (*C*H), 137.3 (*C*H), 140.9 (*C*H), 149.5 (*Ar*), 150.8 (*Ar*H); *m/z* (EI) 150 (15, M), 104 (59, M- NO_2); HRMS $C_7H_6N_2O_2$ calcd. 150.0429, found 150.0427.

(*E*)-1-Methyl-2-(2-nitrovinyl)-1*H*-pyrrole 84m



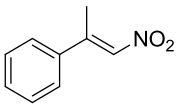
Prepared by General procedure C. *N*-Methyl-pyrrole-2-carboxaldehyde (10.0 mmol) afforded crude **84m** as a black solid which was purified by chromatography (10% EtOAc/pet. ether) to give **84m** (1.30 g, 8.5 mmol, 85% yield) as an orange solid; mp 92-95 ^oC; IR υ_{max} 3133 (C-H), 3093 (C-H), 1609 (C=C), 1528 (N-O), 1489, 1471, 1307 (N-O), 1273, 1245, 1071, 959, 817 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.77 (3H, s, CH_3), 6.27 (1H, dd, *J* = 4.0, 2.5, Ar*H*), 6.80 (1H, dd, *J* = 4.1, 1.3, Ar*H*), 6.92-6.97 (1H, m, Ar*H*), 7.46 (1H, d, *J* = 13.2, C*H*NO_2), 7.99 (1H, d, *J* = 13.2, ArC*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 34.9 (N*C*H_3), 111.2 (*Ar*H), 116.3 (*Ar*H), 125.0 (*Ar*), 127.6 (*Ar*H), 130.8 (Ar*C*H), 131.8 (*C*HNO_2); *m/z* (EI) 152 (54, M); HRMS $C_7H_8N_2O_2$ calcd. 152.0586, found 152.0581.

(*E*)-2-(2-Nitrovinyl)-1-tosyl-1*H*-pyrrole 84n



Prepared by General procedure B. *N*-Tosyl-pyrrole-2-carboxaldehyde (5.0 mmol) afforded crude **84n** as a black oil which was purified by chromatography (20% EtOAc/pet. ether) to give **84n** (2.48 g, 8.5 mmol, 85% yield) as an orange solid; mp 139-140 ^{o}C; IR υ_{max} 3119 (C-H), 1622 (C=C), 1505 (N-O), 1373 (N-O), 1323 (S=O), 1175, 1152, 666 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (3H, s, *Me*), 6.40 (1H, t, *J* = 3.5, Ar*H*), 6.82 (1H, d, *J* = 2.4, Ar*H*), 7.33 (2H, d, *J* = 8.3, Ar*H*), 7.36 (1H, d, *J* = 13.6, ArC*H*), 7.56-7.66 (1H, m, Ar*H*), 7.74 (2H, d, *J* = 8.5, Ar*H*), 8.50 (1H, d, *J* = 13.6, C*H*NO_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.8 (*C*H_3), 113.5 (*Ar*H), 118.7 (*Ar*H), 125.7 (*Ar*), 127.1 (*C*H), 127.2 (*Ar*H), 128.5 (*C*H), 130.6 (*Ar*H), 135.2 (*Ar*), 135.7 (*C*H), 146.3 (*Ar*); *m/z* (EI) 292 (4, M), 249 (9), 155 (43), 91 (100); HRMS $C_{13}H_{12}N_2O_4S$ calcd. 292.0512, found 292.0529.

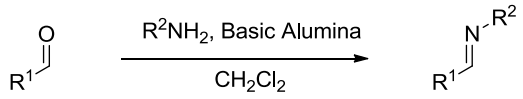
(*E*)-(1-Nitroprop-1-en-2-yl)benzene 286



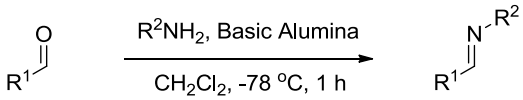
Prepared according to a modified literature procedure.[54a] To a pre-cooled solution of acetic anhydride (32.0 mL, 340.0 mmol) at -20 ^{o}C was added dropwise a solution of 70% nitric acid in water (2.8 mL, 44.0 mmol). The mixture was then allowed to warm to rt (CAUTION – temperature rises rapidly above 0 ^{o}C) and then cooled back to -20 ^{o}C. To this colourless solution was then added dropwise *α*-methylstyrene (2.6 mL, 20.0 mmol) keeping the reaction temperature below -15 ^{o}C. The reaction was then stirred between -10 and -20 ^{o}C for 15 min or until reaction complete as monitored by tlc. Ice/water (15 g) was then added and the mixture was allowed to warm to rt and stirred for 15 min. The pale pink solution was then diluted with sat. brine (5 mL) and extracted with Et_2O (3 x 15 mL). The combined organics were then washed with sat. aq. $NaHCO_3$ 5 x 100 mL) and with sat. brine (25 mL) and dried ($MgSO_4$). The excess solvent was removed *in vacuo* to give crude *β*-nitroacetate (3.75 g, 16.8 mmol, 84% yield) which was re-dissolved in $CHCl_3$ (25 mL) before Et_3N (12.5 mL, 90.0 mmol) was added and the reaction was stirred for 12 h at rt or

until reaction judged complete by tlc analysis. The reaction was then diluted with more $CHCl_3$ (25 mL) and washed with 2.0 M HCl (2 x 50 mL) and sat. brine (25 mL). The resultant organic phase was then dried ($MgSO_4$) and the excess solvent removed to afford, after purification by column chromatography (1% Et_2O/pet. ether), **286** (1.42 g, 8.7 mmol, 44% yield) as a yellow oil which solidified in the freezer; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.65 (3H, s, C*H*$_3$), 7.31 (1H, s, Ar*H*), 7.42-7.49 (5H, m, Ar*H*); ^{1}H NMR data are consistent with literature data.[54a]

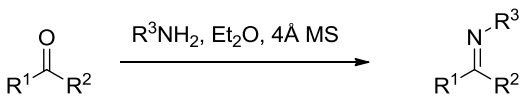
4.2.2 Procedures for preparation of imines



General procedure D: To a mixture of basic alumina (1.0 g per mmol) and amine (limiting reagent) in CH_2Cl_2 (5.0 mL per mmol) under N_2 at rt was added carbonyl compound (1.0 equiv.). The mixture was stirred until reaction complete (typically less than 30 min) as monitored by ^{1}H NMR. Filtration through celite® and removal of solvents *in vacuo* afforded crude imine.

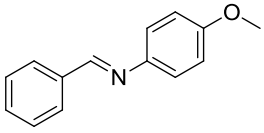


General procedure E: To a mixture of basic alumina (1.0 g per mmol) amine (limiting reagent) in CH_2Cl_2 (5.0 mL per mmol) under N_2 at -78 ^{o}C was added carbonyl compound (1.0 equiv.). The mixture was stirred at -78 ^{o}C for 1 h and then warmed in an ice bath for 5 min before allowing the reaction to warm to rt over 5 min. Filtration through celite® and removal of solvents *in vacuo* afforded crude imine which was used without further purification.



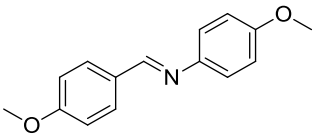
General procedure F: To a flask containing rigorously flame-dried 4Å molecular sieves (1.0 g per mmol) in Et_2O (5.0 mL per mmol) under N_2 at rt was added amine (limiting reagent). After 5 min, carbonyl compound (1.0 equiv.) was added and the mixture was stirred until reaction complete (typically 16 h) as monitored by ^{1}H NMR. Filtration through celite® and removal of solvents *in vacuo* afforded crude imine.

(*E*)-*N*-Benzylidene-4-methoxyaniline 30a



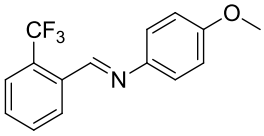
Prepared by General procedure D. Benzaldehyde (10.0 mmol) afforded crude **30a** as a pale yellow solid. Recrystallisation in EtOAc/pet. ether gave **30a** (1.52 g, 7.2 mmol, 72% yield) as off-white flakes; mp 68-69 ^{o}C (Lit.[160] 66-68 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.84 (3H, s, OC*H*$_3$), 6.94 (2H, dm, *J* = 9.1, Ar*H*), 7.24 (2H, dm, *J* = 9.1, Ar*H*), 7.43-7.50 (3H, m, Ar*H*), 7.85-7.92 (2H, m, Ar*H*), 8.49 (1H, s, *H*C=N). ^{1}H NMR data are consistent with literature data.[160]

(*E*)-4-Methoxy-*N*-(4-methoxybenzylidene)aniline 30e



Prepared by General procedure D. 4-Methoxybenzaldehyde (10.0 mmol) afforded crude **30e** as a yellow/orange solid. Recrystallisation in EtOAc/pet. ether gave **30e** (2.03 g, 8.4 mmol, 84% yield) as a pale yellow solid; mp 136-138 ^{o}C (Lit.[161] 137-139 ^{o}C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.83 (3H, s, OC*H*$_3$), 3.87 (3H, s, OC*H*$_3$), 6.92 (2H, dm, *J* = 9.1, Ar*H*), 6.98 (2H, dm, *J* = 8.8, Ar*H*), 7.21 (2H, dm, *J* = 9.1, Ar*H*), 7.83 (2H, dm, *J* = 8.8, Ar*H*), 8.41 (1H, s, *H*C=N). ^{1}H NMR data are consistent with literature data.[162]

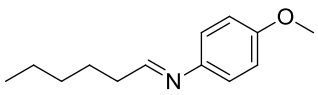
(*E*)-4-Methoxy-*N*-(2-(trifluoromethyl)benzylidene)aniline 30g



Prepared by General procedure D. 2-(Trifluoromethyl)benzaldehyde (15.0 mmol) afforded crude **30g** as a yellow solid. Recrystallisation in EtOAc/pet. ether gave **30g** (2.38 g, 8.5 mmol, 57% yield) as yellow flakes; mp 54-56 ^{o}C; IR υ_{max} 2959 (C-H), 1622 (C=N), 1574, 1502, 1311, 1166, 1105 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.85 (3H, s, OC*H*$_3$), 6.96 (2H, dm, *J* = 9.0, Ar*H*), 7.25-7.30 (2H, m, Ar*H*), 7.55 (1H, t, *J* = 7.5, Ar*H*), 7.65 (1H, t, *J* = 7.6, Ar*H*), 7.73 (1H, d, *J* = 7.9, Ar*H*), 8.44 (1H, d, *J* = 7.9, Ar*H*), 8.83-8.86 (1H, m, N=C*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 55.6 (*C*H_3), 114.6

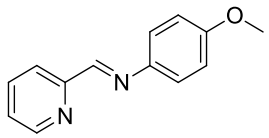
(*Ar*H), 122.7 (*Ar*H) 124.4 (1C, q, *J* = 275.1, *C*F_3), 125.8 (1C, q, *J* = 5.5, *Ar*H), 128.3 (*Ar*H), 129.5 (1C, q, *J* = 31.9, *Ar*CF_3), 130.4 (*Ar*H), 132.2 (*Ar*H), 134.5 (*Ar*), 144.5 (*C*=N), 154.2 (*Ar*H), 158.9 (*Ar*O); *m/z* (EI) 279 (100, M); HRMS $C_{15}H_{12}F_3NO$ calcd. 279.0871, found 279.0866.

(*E*)-*N*-Hexylidene-4-methoxyaniline 30i



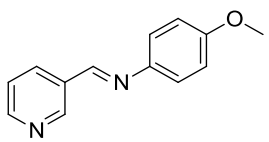
Prepared by General procedure E. *n*Hexanal (0.55 mmol) afforded crude **30i** (115 mg, 0.56 mmol, quantitative yield) as a colourless oil which was used without further purification; IR υ_{max} 1621 (C=N), 1505, 1249, 1165, 1127 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.85 (3H, t, *J* = 7.0, C*H*$_3$), 1.18-1.28 (4H, m, C*H*$_2$), 1.50 (2H, m, C*H*$_2$), 2.28 (2H, m, C*H*$_2$), 3.33 (3H, s, OC*H*$_3$), 6.78 (2H, d, *J* = 8.9, Ar*H*), 7.08 (2H, d, *J* = 8.9, Ar*H*), 7.63 (1H, t, *J* = 7.7, *H*C=N); ^{13}C NMR (100 MHz, C_6D_6) δ 14.0 (*C*H_3), 22.8 (*C*H_2), 25.6 (*C*H_2), 31.6 (*C*H_2), 36.4 (*C*H_2), 54.8 (*C*H_2), 114.4 (*Ar*H), 115.2 (*Ar*H), 121.9 (*Ar*), 145.5 (*C*=N), 163.4 (*Ar*O); compound unstable to mass spec. analysis. ^{1}H NMR data are consistent with literature data.[17]

(*E*)-4-Methoxy-*N*-(pyridin-2-ylmethylene)aniline 30k



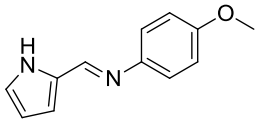
Prepared by General procedure D. 2-Pyridinecarboxaldehyde (15.0 mmol) afforded crude **30k** as a yellow/orange solid. Recrystallisation in EtOAc/pet. ether gave **30k** (1.24 g, 5.8 mmol, 39% yield) as a pale yellow solid; mp 40-42 ^{o}C (Lit.[163] 36-37 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (3H, s, OC*H*$_3$), 6.98 (2H, dm, J = 9.0, Ar*H*), 7.32-7.41 (3H, m, Ar*H*), 7.78-7.86 (1H, m, Ar*H*), 8.21 (1H, dt, J = 8.0, 1.0, Ar*H*), 8.66 (1H, m, N=C*H*), 8.68-8.76 (1H, m, Ar*H*). ^{1}H NMR data are consistent with literature data.[163]

(*E*)-4-Methoxy-*N*-(pyridin-3-ylmethylene)aniline 30l



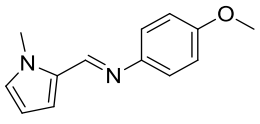
Prepared by General procedure D. 3-Pyridinecarboxaldehyde (5.0 mmol) afforded crude **30l** as a yellow/orange solid. Recrystallisation in Et_2O/pet. ether gave **30l** (2.30 g, 10.8 mmol, 72% yield) as a pale yellow solid; mp 63-65 ^oC; IR υ_{max} 3140 (C-H), 2942 (C-H), 2835 (C-H), 1613 (C=N), 1504, 1365, 1246, 1174, 670 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.84 (3H, s, OC*H*$_3$), 6.92-6.97 (2H, m, Ar*H*), 7.23-7.29 (2H, m, Ar*H*), 7.39 (1H, dd, *J* = 7.9, 4.7, Ar*H*), 8.27 (1H, m, Ar*H*), 8.49-8.53 (1H, m, Ar*H*), 8.67 (1H, dd, *J* = 4.7, 1.5), 8.99 (1H, s); ^{13}C NMR (151 MHz, $CDCl_3$) δ 55.6 (O*C*H$_3$), 114.6 (*Ar*H), 122.5 (*Ar*H), 123.9 (*Ar*H), 132.2 (*Ar*), 134.8 (*Ar*H), 144.3 (*Ar*), 150.9 (*Ar*H), 151.8 (*Ar*H), 155.0 (*C*H=N), 158.9 (*Ar*O); *m/z* (EI) 212 (100, M); HRMS $C_{13}H_{12}N_2O$ calcd. 212.0950, found 212.0951.

(*E*)-*N*-((1*H*-Pyrrol-2-yl)methylene)-4-methoxyaniline 30m



Prepared by General procedure D. Pyrrole-2-carboxaldehyde (10.5 mmol) afforded crude **30m** (2.40 g) as a yellow/orange solid. Recrystallisation in 50% Et_2O/pet. ether (12.5 mL per gram) gave **30m** (1.43 g, 7.2 mmol, 68% yield) as a pale yellow solid; mp 82-84 ^oC; IR υ_{max} 3205 (C-H), 2963 (C-H), 2835 (C-H), 1616 (C=N), 1502, 1410, 1239, 1203, 1132, 1029, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.82 (3H, s, OC*H*$_3$), 6.30 (1H, dd, *J* = 3.8, 2.8, Ar*H*), 6.64 (1H, dd, *J* = 3.5, 1.3 Ar*H*), 6.91 (2H, dm, *J* = 8.8, Ar*H*), 6.94-6.97 (1H, m, Ar*H*), 7.17 (2H, dm, *J* = 8.8, Ar*H*), 8.26 (1H, s, *H*C=N); ^{13}C NMR (151 MHz, $CDCl_3$) δ 55.6 (*C*H$_3$), 110.4 (*Ar*H), 114.6 (*Ar*H), 116.2 (*Ar*H), 122.1 (*Ar*H), 123.1 (*Ar*H), 131.0 (*Ar*), 144.9 (*Ar*), 148.5 (*C*H=N), 157.9 (*Ar*O); *m/z* (EI) 200 (100, M); HRMS $C_{12}H_{12}N_2O$ calcd. 200.0950, found 200.0939.

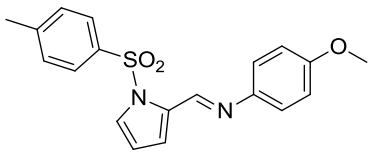
(*E*)-4-Methoxy-*N*-((1-methyl-1*H*-pyrrol-2-yl)methylene)aniline 30n



Prepared by General procedure D. *N*-Methyl-pyrrole-2-carboxaldehyde (5.0 mmol) afforded crude **30n** as a yellow/orange solid. Recrystallisation in EtOAc/pet. ether gave **30n** (685 mg, 3.2 mmol, 64% yield) as a pale yellow solid; mp 58-59 ^oC; IR υ_{max} 2944 (C-H), 2835 (C-H), 1622 (C=N), 1504, 1426, 1244 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.82 (3H, s, OC*H*$_3$), 4.05 (3H, s, NC*H*$_3$), 6.18-6.23 (1H, m, Ar*H*),

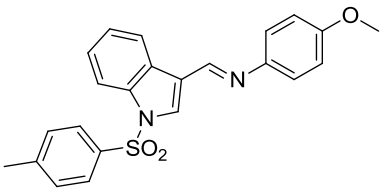
6.65 (1H, dd, *J* = 3.9, 1.8, Ar*H*), 6.78 (1H, t, *J* = 2.3, Ar*H*), 6.91 (2H, dm, *J* = 8.8, Ar*H*), 7.13 (2H, dm, *J* = 8.8, Ar*H*), 8.30 (1H, s, *H*C=N); ^{13}C NMR (151 MHz, $CDCl_3$) δ 37.0 (N*C*H$_3$), 55.6 (O*C*H$_3$), 108.7 (*Ar*H), 114.5 (*Ar*H), 118.0 (*Ar*H), 121.9 (*Ar*H), 128.8 (*Ar*H), 130.6 (*Ar*), 146.1 (*Ar*), 149.6 (*C*H=N), 157.6 (*Ar*O); *m/z* (EI) 214 (100, M); HRMS $C_{13}H_{14}N_2O$ calcd. 214.1106, found 214.1109.

(*E*)-4-Methoxy-*N*-((1-tosyl-1*H*-pyrrol-2-yl)methylene)aniline 30k



Prepared by General procedure D. *N*-Tosyl-pyrrole-2-carboxaldehyde (10.0 mmol) afforded crude **30k** (3.30 g**)** as a yellow solid. Recrystallisation in EtOAc/pet. ether gave **30k** (2.62 g, 7.4 mmol, 74% yield) as a pale yellow solid; mp 76-79 ^{o}C; IR υ_{max} 2994 (C-H), 2834 (C-H), 1614 (C=N), 1373 (S=O), 1130 (S=O), 726, 671 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.38 (3H, s, ArC*H*$_3$), 3.84 (3H, s, OC*H*$_3$), 6.38 (1H, t, *J* = 3.6, Ar*H*), 6.93 (2H, dm, *J* = 8.9, Ar*H*), 7.10 (1H, dd, *J* = 3.7, 1.2, Ar*H*), 7.18 (2H, dm, *J* = 8.9, Ar*H*), 7.27 (2H, d, *J* = 7.9, Ar*H*), 7.46 (1H, dd, *J* = 3.2, 1.7, Ar*H*), 7.68 (2H, dm, *J* = 8.5, Ar*H*), 8.89 (1H, s, N=C*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.8 (*C*H$_3$), 55.6 (O*C*H$_3$), 113.3 (*Ar*H), 114.5 (*Ar*H), 117.1 (*Ar*H), 122.5 (*Ar*H), 126.2 (*Ar*H), 126.9 (*Ar*H), 130.3 (*Ar*H), 133.2 (*Ar*), 135.9 (*Ar*), 144.8 (*Ar*), 145.7 (*Ar*), 147.7 (*C*H=N), 158.5 (*Ar*O); *m/z* (ESI^{+}) 355 (27, M+H), 199 (100, M-Ts); HRMS $C_{19}H_{18}N_2O_3SH^{+}$ calcd. 355.1116, found 355.1111.

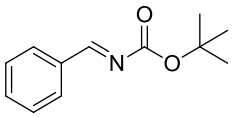
(*E*)-4-Methoxy-*N*-((1-tosyl-1*H*-indol-3-yl)methylene)aniline 30q



Prepared by General procedure A. *N*-Tosyl-indole-3-carboxaldehyde (5.0 mmol) afforded crude **30q** (1.80 g) as a yellow solid. Recrystallisation in EtOAc/pet. ether gave **30q** (1.40 g, 3.5 mmol, 74% yield) as an off-white solid; mp 92-95 ^{o}C; IR υ_{max} 2836 (C-H), 1616 (C=N), 1505, 1365 (S=O), 1167 (S=O), 1126, 795, 672 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.35 (3H, s, ArC*H*$_3$), 3.84 (3H, s, OC*H*$_3$), 6.94 (2H, dm, *J* = 9.0, Ar*H*), 7.22-7.26 (4H, m, Ar*H*), 7.33-7.36 (1H, m, Ar*H*), 7.37-7.41 (1H, m,

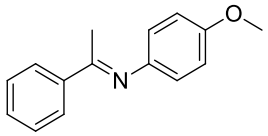
Ar*H*), 7.81 (2H, dm, *J* = 8.3, Ar*H*), 7.97 (1H, s, Ar*H*), 7.99 (1H, dm, *J* = 8.1, Ar*H*), 8.52 (1H, dm, *J* = 7.8), 8.62 (1H, s, N=C*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.7 (Ar*C*H$_3$), 55.6 (O*C*H$_3$), 113.4 (*Ar*H), 114.5 (*Ar*H), 121.2 (*Ar*), 122.2 (*Ar*H), 123.4 (*Ar*H), 124.4 (*Ar*H), 125.9 (*Ar*H), 127.1 (*Ar*H), 127.9 (*Ar*), 130.2 (*Ar*H), 130.7 (*Ar*H), 134.9 (*Ar*), 135.7 (*Ar*), 145.4 (*Ar*), 145.6 (H*C*=N), 151.4 (*Ar*H), 158.3 (*Ar*O); *m/z* 404 (100, M); HRMS $C_{23}H_{20}N_2O_3S$ calcd. 404.1195, found 404.1188.

(*E*)-*tert*-Butyl benzylidenecarbamate 41a



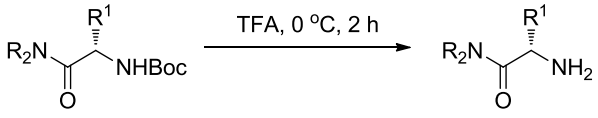
Prepared according to literature procedure.[164] Benzaldehyde (10.0 mmol) gave **41a** (1.63 g, 7.9 mmol, 79% yield) as a colourless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.59 (9H, s, C(C*H*$_3$)$_3$), 7.47 (2H, t, *J* = 7.7, Ar*H*), 7.57 (1H, t, *J* = 7.5, Ar*H*), 7.92 (2H, d, *J* = 8.1, Ar*H*), 8.88 (1H, s, *H*C=N). ^{1}H NMR data are consistent with literature data.[164]

(*E*)-4-Methoxy-*N*-(1-phenylethylidene)aniline 291



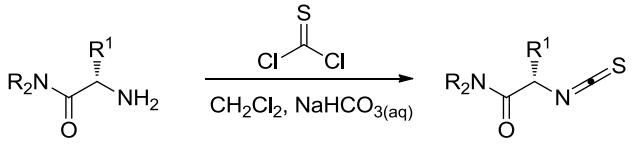
Prepared according to General procedure F. Acetophenone (10.0 mmol) gave crude **291** as an orange solid. Recrystallisation in 5% EtOAc/pet. ether (15 mL per gram) afforded **291** (1.49 g, 6.6 mmol, 66% yield) as a pale yellow solid; mp 83-85 ^{o}C (Lit.[165] 84-85 ^{o}C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.26 (3H, s, N=CC*H*$_3$), 3.82 (3H, s, OC*H*$_3$), 6.76 (2H, dm, *J* = 4.5, Ar*H*), 6.92 (2H, dm, *J* = 8.8, Ar*H*), 7.42-7.47 (3H, m, Ar*H*), 7.95-7.98 (2H, m, Ar*H*). ^{1}H NMR data are consistent with literature data.[165]

4.2.3 Preparation of catalysts

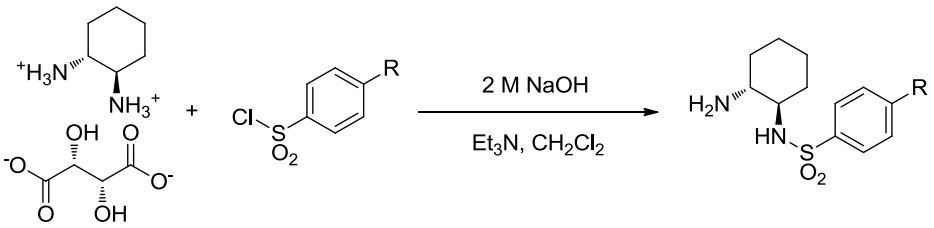


General Procedure G: A solution of cold (ice bath, 0 ^{o}C) TFA (10 mL per mmol) was added to a pre-cooled flask (ice bath, 0 ^{o}C) containing *N*-Boc-amine (limiting reagent) and stirred for 2 h. The excess solvent was then removed *in vacuo* and the concentrated residue was cooled to 0 ^{o}C. To this residue was added 2.0 M NaOH (20

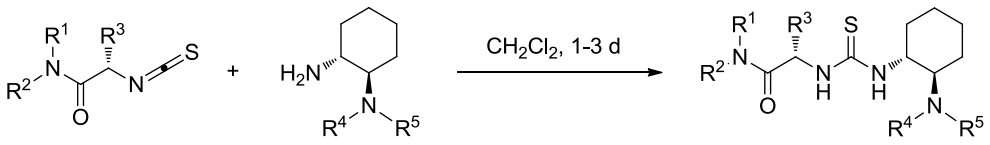
mL per mmol) and 5% MeOH/CH_2Cl_2 (30 mL per mmol) and the mixture was stirred for 15 min. The biphasic mixture was then separated and the aqueous layer was re-extracted with more 5% MeOH/CH_2Cl_2 (2 x 30 mL per mmol). The combined organics were dried (Na_2SO_4) and the excess solvent was removed *in vacuo* to give amine.



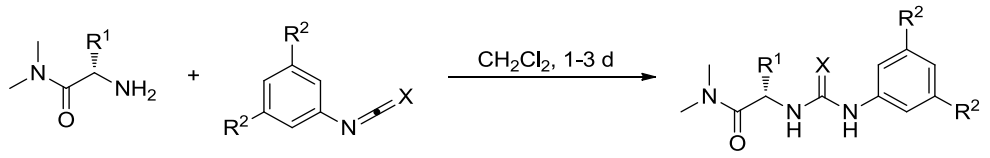
General Procedure H: Modification of literature procedure.[33] A solution of amine (limiting reagent) in CH_2Cl_2 (10 mL per mmol) and sat. aq. $NaHCO_3$ (10 mL per mmol) was cooled to 3 ^oC (ice bath) and stirred for 15 min. Stirring was then stopped and thiophosgene (1.5 equiv.) was syringed directly into the organic layer. The mixture was then vigorously stirred for 1 h at 3 ^oC. The reaction was extracted with CH_2Cl_2 (2 x 10 mL per mmol), dried ($MgSO_4$) and the excess solvent removed to give pure product.



General Procedure I: Modification of literature procedure.[132] To a solution of (*R*,*R*)-diaminocyclohexane *L*-tartrate (1.5 equiv.) in 2.0 M NaOH (2.0 mL per mmol) was added Et_3N (2.0 equiv.) and CH_2Cl_2 (15 mL per mmol). The mixture was cooled to 0 ^oC and a solution of sulfonyl chloride (limiting reagent) in CH_2Cl_2 (11 mL per mmol) was added dropwise over 30 min. After complete addition the reaction was allowed to warm to rt and stirred for 16 h. The reaction was then extracted with 2.0 M HCl (3 x 5 mL per mmol). The combined aqueous extracts were basified to ~ pH 9 with NaOH pellets to give a cloudy white mixture which was then extracted with CH_2Cl_2 (3 x 5 mL per mmol). The combined organics were then dried ($MgSO_4$) and the excess solvent removed *in vacuo* to give pure product.

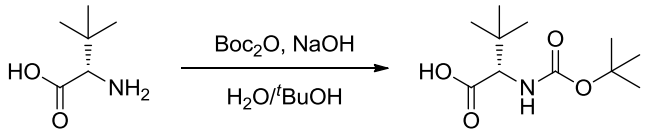


General Procedure J: To a solution of *iso*thiocyanate (limiting reagent) in CH_2Cl_2 (5 mL per mmol) at room temperature was added amine (1.2 equiv.) and the reaction was stirred at rt for 3 days or until reaction complete, as judged by tlc analysis. The excess solvent was then removed *in vacuo* to give the crude product.



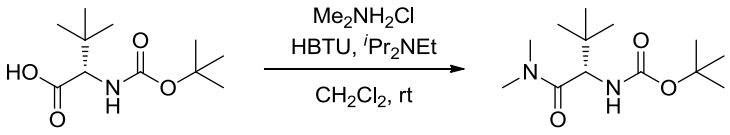
General Procedure K: To a solution of *iso*(thio)cyanate (limiting reagent) in CH_2Cl_2 (5 mL per mmol) at room temperature was added amine (1.2 equiv.) and the reaction was stirred at rt for 3 days or until reaction complete, as judged by tlc analysis. The excess solvent was then removed *in vacuo* to give the crude product.

(*S*)-2-((*tert*-Butoxycarbonyl)amino)-3,3-dimethylbutanoic acid 241



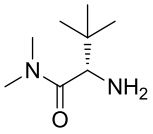
Prepared according to literature procedure.[166] *L-tert*-leucine (40.0 mmol) gave **241** (7.40 g, 32.0 mmol, 80% yield) as a white solid; mp 108-110 °C (Lit.[166] 122-123 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.02 (9H, s, C(C*H*$_3$)$_3$), 1.44 (9H, s, C(C*H*$_3$)$_3$), 4.12 (1H, d, *J* = 9.6, C*H*^{t}Bu), 5.09 (1H, d, *J* = 9.2, N*H*); ^{1}H NMR_{Rot} δ 3.89 (1H, br. s), 5.86 (1H, br. s,). ^{1}H NMR data are consistent with literature data.[166]

(*S*)-*tert*-butyl (1-(dimethylamino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate 242



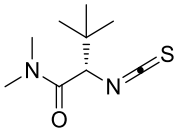
Prepared according to literature procedure.[167] *N*-Boc-*L-tert*-leucine **241** (2.0 mmol) gave **242** (410 mg, 1.6 mmol, 80% yield) as a colourless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.97 (9H, s, C(C*H*$_3$)$_3$), 1.42 (9H, s, C(C*H*$_3$)$_3$), 2.96 (3H, s, N(C*H*$_3$)$_2$), 3.13 (3H, s, N(C*H*$_3$)$_2$), 4.52 (1H, d, *J* = 9.8, C*H*^{t}Bu), 5.34 (1H, d, *J* = 9.8, N*H*). ^{1}H NMR data are consistent with literature data.[167]

(*S*)-2-Amino-*N*,*N*,3,3-tetramethylbutanamide 243



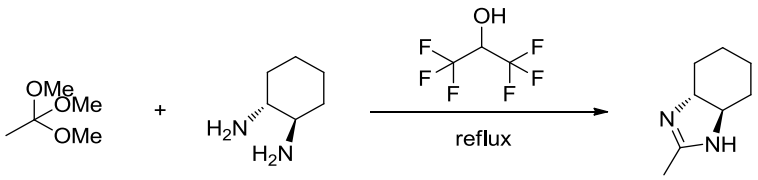
Prepared by General procedure G. Boc-protected amine **242** (2.09 mmol) gave **243** (248 mg, 1.57 mmol, 75% yield) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (9H, s, C(C*H*$_3$)$_3$), 2.84 (3H, s, N(C*H*$_3$)$_2$), 2.97 (3H, s, N(C*H*$_3$)$_2$), 3.42 (1H, s, C*H*^{t}Bu); ^{1}H NMR data are consistent with literature data. [167]

(*S*)-2-Isothiocyanato-*N*,*N*,3,3-tetramethylbutanamide 244



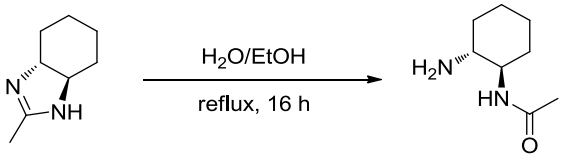
Prepared by General procedure H. Amine **243** (1.57 mmol) gave **244** (342 mg, 1.72 mmol, quantitative yield) as a colourless oil; IR υ_{max} 2970 (C-H), 2037 (N=C=S), 1641 (C=O), 1496, 1473, 1398, 1137 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.09 (9H, s, C(C*H*$_3$)$_3$), 3.01 (3H, s, N(C*H*$_3$)$_2$), 3.08 (3H, s, N(C*H*$_3$)$_2$), 4.27 (1H, s, C*H*^{t}Bu); ^{13}C NMR (151 MHz, $CDCl_3$) δ 26.6 (C(*C*H$_3$)$_3$), 36.5 (N(*C*H$_3$)$_2$), 37.7 (*C*Me$_3$), 38.4 (N(*C*H$_3$)$_2$), 64.2 (*C*H^{t}Bu), 135.6 (N=*C*=S), 166.5 (*C*=O); *m/z* (CI) 201 (72, M+H), 144 (100, M+H-^{t}Bu); HRMS $C_9H_{16}N_2OSH$ calcd. 201.1062, found 201.1053.

(3a*R*,7a*R*)-2-Methyl-3a,4,5,6,7,7a-hexahydro-1H-benzo[*d*]imidazole 247



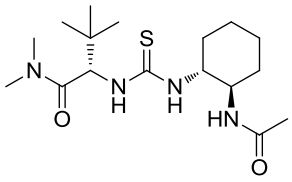
Prepared according to literature procedure.[129] Trimethyl orthoacetate (0.90 mmol) gave **247** (151 mg, 1.09 mmol, quantitative yield) as a colourless solid which was used in the next step without further purification; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.24-1.36 (2H, m, *Cy*), 1.41-1.53 (2H, m, *Cy*), 1.81-1.91 (2H, m, *Cy*), 2.10 (3H, s, C*H*$_3$), 2.17 (2H, br. d, *J* = 12.0, *Cy*), 3.20-3.28 (2H, m, *Cy*); ^{1}H NMR data are consistent with literature data.[129]

_N_-((1_R_,2_R_)-2-Aminocyclohexyl)acetamide 248



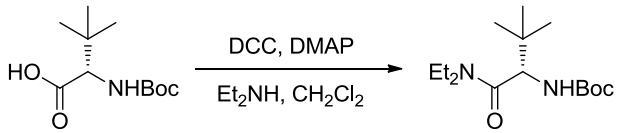
Prepared according to literature procedure.[128] Benzoimidazole **247** (0.90 mmol) gave **248** (133 mg, 0.85 mmol, 95% yield) as a colourless solid which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02-1.36 (4H, m, *Cy*), 1.63-1.74 (2H, m, *Cy*), 1.88-1.97 (2H, m, *Cy*), 1.98 (3H, s, C*H*$_3$), 2.36 (1H, td, *J* = 10.4, 4.0, C*H*NH$_2$), 3.41-3.53 (1H, m, C*H*NHCO), 6.06 (1H, br. d, *J* = 6.5, N*H*CO); ^{1}H NMR data are consistent with literature data.[128]

(_S_)-2-(3-((1_R_,2_R_)-2-Acetamidocyclohexyl)thioureido)-_N_,_N_,3,3-tetramethylbutanamide 54



Prepared according to literature procedure (21-60% yield),[33] or **by General procedure J.** Isothiocyanate **244** (0.80 mmol) gave crude **54** (295 mg) which was purified by recrystallisation (EtOAc/pet. ether) to give **54** (206 mg, 0.58 mmol, 72% yield) as a white solid; mp 208-209 ^{o}C; $[\alpha]_D^{25}$ = +58.7 ^{o} (c = 1.00, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (9H, s, C(C*H*$_3$)$_3$), 1.22-1.40 (4H, m, *Cy*), 1.75-1.82 (2H, m, *Cy*), 1.98 (3H, s, COC*H*$_3$), 2.11 (1H, br. d, *J* = 9.5, *Cy*), 2.21 (1H, br. d, *J* = 12.5, *Cy*), 2.97 (3H, s, NC*H*$_3$), 3.28 (3H, s, NC*H*$_3$), 3.57-3.67 (1H, m, C*H*N), 4.28-4.42 (1H, m, C*H*N), 5.57 (1H, d, *J* = 9.5, C*H*^{t}Bu), 6.62-6.76 (1H, br. s, N*H*), 6.93 (1H, d, *J* = 9.0, N*H*), 7.04 (1H, d, *J* = 7.8, N*H*). ^{1}H NMR data are consistent with literature data.[33]

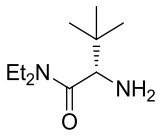
(_S_)-_tert_-Butyl (1-(diethylamino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate 249



Prepared according to literature procedure.[102] *N*-Boc-*L*-*tert*-leucine **241** (3.00 mmol) gave, after purification by column chromatography (15% EtOAc/pet. ether), **249** (387 mg, 1.35 mmol, 45% yield) as a colourless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ

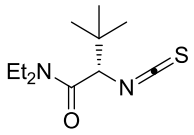
1.02 (9H, s, C(CH_3)$_3$), 1.44 (9H, s, C(CH_3)$_3$), 4.12 (1H, d, J = 9.6, CH^{t}Bu), 5.09 (1H, d, J = 9.2, NH); ^{1}H NMR$_{Rot}$ δ 3.89 (1H, br. s), 5.86 (1H, br. s,). ^{1}H NMR data are consistent with literature data.[102]

(*S*)-2-Amino-*N*,*N*-diethyl-3,3-dimethylbutanamide250



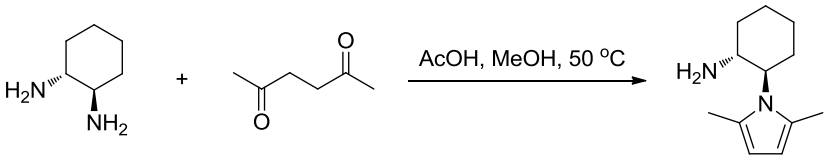
Prepared by General procedure G. Boc-protected amine **249** (0.47 mmol) gave **250** (75 mg, 0.40 mmol, 86% yield) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (9H, s, C(CH_3)$_3$), 1.13 (3H, t, J = 7.2, CH_2CH_3), 1.20 (3H, t, J = 7.2, CH_2CH_3), 3.09 (1H, m, CH_2Me), 3.20 (1H, m, CH_2Me), 3.39 (1H, s, CH^{t}Bu), 3.59 (1H, m, CH_2Me), 3.70 (1H, m, CH_2Me); ^{1}H NMR data are consistent with literature data.[102]

(*S*)-*N*,*N*-Diethyl-2-isothiocyanato-3,3-dimethylbutanamide 251



Prepared by General procedure H. Amine **250** (0.40 mmol) gave **251** (97 mg, 0.42 mmol, quantitative yield) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (9H, s, C(CH_3)$_3$), 1.15 (3H, t, J = 7.1, CH_2CH_3), 1.23 (3H, t, J = 7.3, CH_2CH_3), 3.18 (1H, dq, J = 14.2, 7.3, CH_2CH$_3$), 3.27 (1H, dq, J = 14.5, 7.3, CH_2CH$_3$), 3.44 (1H, dq, J = 14.8, 6.9, CH_2CH$_3$), 3.62-3.79 (1H, m, CH_2CH$_3$); ^{1}H NMR data are consistent with literature data.[102]

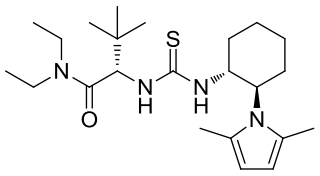
(1*R*,2*R*)-2-(2,5-Dimethyl-1*H*-pyrrol-1-yl)cyclohexanamine 252



Prepared according to literature procedure.[168] (1*R*,2*R*)-1,2-Diaminocyclohexane (2.19 mmol) afforded, after purification by column chromatography (5% MeOH/CH_2Cl_2), **252** (310 mg, 1.61 mmol, 74% yield) as a yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.16-1.25 (1H, m, *Cy*), 1.31-1.42 (2H, m, *Cy*), 1.75-1.82 (1H, m, *Cy*), 1.82-1.96 (3H, m, *Cy*), 2.01-2.09 (1H, m, *Cy*), 2.23 (3H, s, ArCH_3), 2.36 (3H, s,

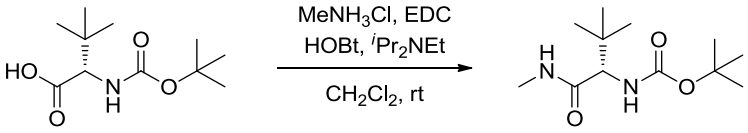
ArCH_3), 3.26 (1H, td, *J* = 10.6, 4.0, Cy*H*N), 3.60 (1H, apt. td, *J* = 11.1, 4.6, Cy*H*N), 5.76 (2H, d, *J* = 19.2, NH_2); ^{1}H NMR data are consistent with literature data.[168]

(*S*)-2-(3-((1*R*,2*R*)-2-(2,5-Dimethyl-1*H*-pyrrol-1-yl)cyclohexyl)thioureido)-*N*,*N*-diethyl-3,3-dimethylbutanamide 191



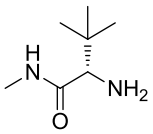
Prepared according to literature procedure.[102] Isothiocyanate **251** (0.40 mmol) gave, after purification by column chromatography (10% EtOAc/pet. ether), **191** (117 mg, 0.28 mmol, 70 % yield) as a pink solid; mp 99-101 ^{o}C; $[\alpha]_D^{25}$ = -26.2 ^{o} (c = 1.025, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (9H, s, C(CH_3)$_3$), 1.10 (3H, t, *J* = 7.1, CH_2CH_3), 1.19-1.23 (1H, m, *Cy*), 1.26 (3H, t, *J* = 7.1, CH_2CH_3), 1.34-1.51 (2H, m, *Cy*), 1.79-2.00 (4H, m, *Cy*), 2.22 (3H, br. s, ArCH_3), 2.35 (3H, br. s, ArCH_3), 2.53 (1H, br. d, *J* = 12.6, *Cy*), 3.07 (1H, dq, *J* = 13.7, 7.0, CH_2Me), 3.33 (1H, dq, *J* = 14.7, 7.1, CH_2Me), 3.58-3.72 (2H, m, CH_2Me), 3.76-3.87 (1H, m, *Cy*), 4.29-4.46 (1H, m, *Cy*), 5.43 (1H, br. s, C*H*^{t}Bu), 5.64 (1H, br. s, N*H*), 5.71 (2H, s, Ar*H*), 6.28 (1H, br. d, *J* = 9.5, N*H*). ^{1}H NMR data are consistent with literature data.[102]

(*S*)-*tert*-Butyl (3,3-dimethyl-1-(methylamino)-1-oxobutan-2-yl)carbamate



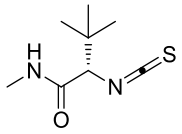
Prepared according to literature procedure.[169] *N*-Boc-*L*-*tert*-leucine **241** (1.50 mmol) gave the title compound (302 mg, 1.24 mmol, 82% yield) as a white solid which was used without further purification; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (9H, s, C(CH_3)$_3$), 1.44 (9H, s, C(CH_3)$_3$), 2.81 (3H, d, *J* = 4.8, NHCH_3), 3.86 (1H, d, *J* = 9.6, C*H*^{t}Bu), 5.35 (1H, br. d, *J* = 9.5, N*H*Boc), 6.17 (1H, br. s, N*H*Me). ^{1}H NMR data are consistent with literature data.[169]

(*S*)-2-Amino-*N*,3,3-trimethylbutanamide



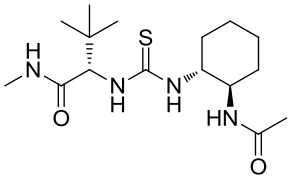
Prepared by General procedure G. (*S*)-*tert*-Butyl (3,3-dimethyl-1-(methylamino)-1-oxobutan-2-yl)carbamate (2.09 mmol) gave the title compound (248 mg, 1.57 mmol, 75% yield) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (9H, s, C(C*H*$_3$)$_3$), 2.82 (3H, d, *J* = 4.9, NHC*H*$_3$), 3.10 (1H, s, C*H*^{t}Bu), 7.28 (2H, br. s, N*H*$_2$); ^{1}H NMR data are consistent with literature data. [170]

(*S*)-2-Isothiocyanato-*N*,3,3-trimethylbutanamide



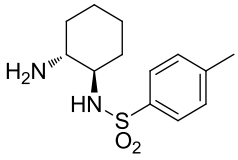
Prepared by General procedure H. (*S*)-2-Amino-*N*,3,3-trimethylbutanamide (2.15 mmol) gave the title compound (384 mg, 2.06 mmol, 96% yield) as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (9H, s, C(C*H*$_3$)$_3$), 2.89 (3H, d, *J* = 4.8, NHC*H*$_3$), 4.07 (1H, s, C*H*^{t}Bu), 6.08 (1H, s, N*H*); ^{1}H NMR data are consistent with literature data.[169]

(*S*)-2-(3-((1*R*,2*R*)-2-acetamidocyclohexyl)thioureido)-*N*,3,3-trimethylbutanamide 265



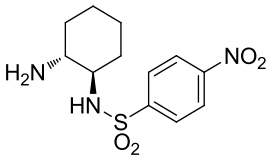
Prepared using same procedure as for **54**.[33] (*S*)-2-Isothiocyanato-*N*,3,3-trimethyl butanamide (0.70 mmol) gave crude **265** (209 mg) which was purified by column chromatography to give **265** (150 mg, 0.44 mmol, 63% yield) as a white solid; mp 149-150 ^{o}C; $[\alpha]_D^{25}$ = +35.0 ^{o} (c = 0.995, $CHCl_3$); IR υ_{max} 3282, 2934 (C-H), 1644 (C=O), 1531 (N-H), 1321 (S=O), 1156 (S=O), 664 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.04 (9H, s, C(C*H*$_3$)$_3$), 1.21-1.42 (4H, m, *Cy*), 1.80 (2H, br. d, *J* = 5.3, *Cy*), 1.94 (3H, s, COC*H*$_3$), 2.01-2.07 (1H, m, *Cy*), 2.13-2.21 (1H, m, *Cy*), 2.78 (3H, d, *J* = 4.9, NHC*H*$_3$), 3.48-3.71 (1H, m, C*H*), 4.45 (1H, br. s, C*H*), 4.75 (1H, br. s, C*H*^{t}Bu), 6.19 (1H, br. s, N*H*), 6.87 (1H, br. s, N*H*), 7.47 (2H, br. s, N*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 23.4 (*C*H$_3$), 24.9 (*C*H$_2$), 25.0 (*C*H$_2$), 26.2 (*C*H$_3$), 27.0 (C(*C*H$_3$)$_3$), 32.6 (2C, br, *C*H$_2$), 34.5 (*C*Me$_3$), 56.3 (2C, br, *C*HN), 66.3 (*C*H^{t}Bu), 171.8 (2C, *C*=O), 183.9 (*C*=S); *m/z* (ESI$^+$) 365 (96, M+Na), 312 (100, M-NMe$_2$); HRMS $C_{15}H_{27}N_3O_2SNa^+$ calcd. 365.1987, found 365.1998.

_N_-((1_R_,2_R_)-2-aminocyclohexyl)-4-methylbenzenesulfonamide



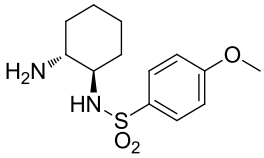
Prepared by General procedure I. (1*R*,2*R*)-1,2-Diaminocyclohexane L-tartrate (34.1 mmol) gave the title compound (5.18 g, 19.3 mmol, 85% yield) as a white solid; mp 97-99 ^{o}C (Lit.[171] 108-110 ^{o}C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.01-1.23 (4H, m, *Cy*), 1.54-1.67 (2H, m, *Cy*), 1.74-1.84 (1H, m, *Cy*), 1.88-1.95 (1H, m, *Cy*), 2.36 (1H, apt. td, *J* = 10.4, 4.0, *Cy*), 2.42 (3H, s, C*H*$_3$), 2.63 (1H, apt. td, *J* = 10.3, 4.2, *Cy*), 7.29 (2H, d, *J* = 7.9, Ar*H*), 7.77 (2H, dm, *J* = 8.3, Ar*H*). ^{1}H NMR data are consistent with literature data.[132]

_N_-((1_R_,2_R_)-2-aminocyclohexyl)-4-nitrobenzenesulfonamide



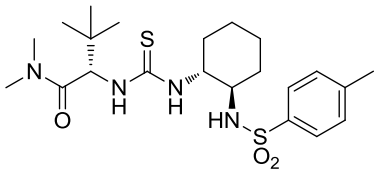
Prepared by General procedure I. (1*R*,2*R*)-1,2-Diaminocyclohexane *L*-tartrate (5.68 mmol) gave the title compound (860 mg, 2.87 mmol, 76% yield) as a yellow solid; mp 159-161 ^{o}C (Lit.[172] 177.5-178 ^{o}C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.05-1.27 (4H, m, *Cy*), 1.59-1.70 (2H, m, *Cy*), 1.86-1.96 (2H, m, *Cy*), 2.40 (1H, apt. td, *J* = 10.5, 4.0, *Cy*), 2.70 (1H, apt. td, *J* = 10.4, 4.1, *Cy*), 8.10 (2H, dm, *J* = 8.8, Ar*H*), 8.36 (2H, dm, *J* = 8.8, Ar*H*). ^{1}H NMR data are consistent with literature data.[172]

_N_-((1_R_,2_R_)-2-aminocyclohexyl)-4-methoxybenzenesulfonamide



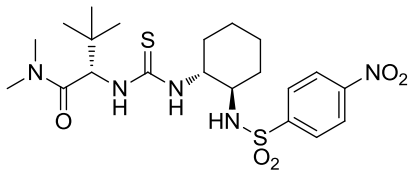
Prepared by General procedure I. (1*R*,2*R*)-1,2-Diaminocyclohexane *L*-tartrate (5.68 mmol) gave the title compound (859 mg, 3.02 mmol, 80% yield) as a white solid; mp 90-92 ^{o}C (Lit.[173] 96-98 ^{o}C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.01-1.25 (4H, m, C*y*), 1.56-1.67 (2H, m, C*y*), 1.78-1.86 (1H, m, C*y*), 1.88-1.94 (1H, m C*y*), 2.30-2.37 (1H, m, C*y*), 2.60 (1H, m, C*y*), 3.87 (3H, s, OC*H*$_3$), 6.97 (2H, dm, *J* = 8.8, Ar*H*), 7.82 (2H, dm, *J* = 8.8, Ar*H*). ^{1}H NMR data are consistent with literature data.[173]

(*S*)-*N*,*N*,3,3-Tetramethyl-2-(3-((1*R*,2*R*)-2-(4-methylphenylsulfonamido)cyclohexyl)thioureido)butanamide 266



Prepared by General procedure J. Isothiocyanate **244** (0.80 mmol) afforded, after purification by column chromatography (5% MeOH/CH_2Cl_2), **266** (362 mg, 0.77 mmol, 96% yield) as a white solid; mp 84-86 ^oC; $[\alpha]_D^{25}$ = +63.8 ^{o} (c = 1.015, $CHCl_3$); IR υ_{max} 3311, 2934 (C-H), 1622 (C=O), 1528, 1318 (S=O), 1156 (S=O), 1091, 661 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.02 (9H, s, C(C*H*$_3$)$_3$), 1.05-1.16 (2H, m, *Cy*), 1.21-1.35 (2H, m, *Cy*), 1.56-1.70 (2H, m, *Cy*), 1.97 (1H, apt. d, *J* = 11.9, *Cy*), 2.07 (1H, apt. d, *J* = 11.7, *Cy*), 2.41 (3H, s, C*H*$_3$), 2.84-2.93 (1H, m, *Cy*), 2.98 (3H, s, N(C*H*$_3$)$_2$), 3.28 (3H, s, N(C*H*$_3$)$_2$), 4.21-4.34 (1H, m, *Cy*), 5.69 (1H, br. d, *J* = 9.2, C*H*^{t}Bu), 6.11 (1H, br. d, *J* = 7.0, N*H*), 6.63-6.82 (2H, br. m, N*H*), 7.22-7.29 (2H, m, Ar*H*), 7.69 (2H, d, *J* = 8.1, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.7 (Ar*C*H$_3$), 24.5 (*C*H$_2$), 24.7 (*C*H$_2$), 26.8 (C(*C*H$_3$)$_3$), 33.0 (*C*H$_2$), 34.0 (*C*H$_2$), 35.9 (N*C*H$_3$), 36.6 (*C*Me$_3$), 38.9 (N*C*H$_3$), 56.8 (*C*H), 59.0 (*C*H), 59.8 (*C*H), 127.1 (*Ar*H), 129.7 (*Ar*H), 138.4 (*Ar*), 143.1 (*Ar*), 172.2 (*C*=O), 183.8 (*C*=S); *m/z* (ESI^+) 491 (100, M+Na), 424 (54, M–Me$_2$N); HRMS $C_{22}H_{36}N_4O_3S_2Na^+$ calcd. 491.2127, found 491.2119.

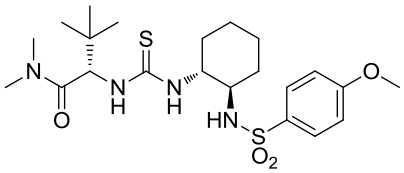
(*S*)-*N*,*N*,3,3-Tetramethyl-2-(3-((1*R*,2*R*)-2-(4-nitrophenylsulfonamido)cyclohexyl)thioureido)butanamide 267



Prepared by General procedure J. Isothiocyanate **244** (0.82 mmol) gave crude **267** (423 mg) which was purified by column chromatography (5% MeOH/CH_2Cl_2) to give **267** (403 mg, 0.81 mmol, 99% yield) as a yellow solid; mp 197-199 ^oC; $[\alpha]_D^{25}$ = +72.5 ^{o} (c = 1.00, $CHCl_3$); IR υ_{max} 3336, 3067, 2937 (C-H), 2865 (C-H), 1641 (C=O), 1529 (N-O), 1349, 1307, 1159 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.02 (9H, s, C(C*H*$_3$)$_3$), 1.09-1.17 (2H, m *Cy*), 1.20-1.35 (2H, m, *Cy*), 1.62 (1H, br. d, *J* = 13.4, *Cy*), 1.68 (1H, br. d, *J* = 13.4, *Cy*), 1.90 (1H, br. d, *J* = 13.4, *Cy*), 2.08 (1H, br. d, *J* =

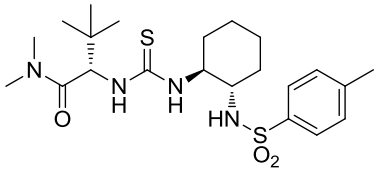
12.4, *Cy*), 2.98-3.04 (1H, m, *Cy*), 3.06 (3H, s, N(*C*H$_3$)$_2$), 3.28 (3H, s, N(*C*H$_3$)$_2$), 4.28-4.37 (1H, m, *Cy*), 5.68 (1H, br. d, *J* = 8.7, C*H*^{t}Bu), 6.31 (1H, br. s, N*H*), 6.88 (1H, br. d, *J* = 9.2, N*H*), 7.61 (1H, br. s, N*H*), 8.04 (2H, d, *J* = 8.8, Ar*H*), 8.32 (2H, d, *J* = 9.2, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 24.4 (*C*H$_2$), 24.7 (*C*H$_2$), 26.8 (*C*H$_3$), 32.8 (*C*H$_2$), 34.1 (*C*H$_2$), 36.0 (N*C*H$_3$), 36.7 (*C*Me$_3$), 38.9 (N*C*H$_3$), 56.6 (C*H*), 59.3 (C*H*), 60.0 (C*H*), 124.4 (*Ar*H), 128.2 (*Ar*H), 147.8 (*Ar*), 149.8 (*Ar*), 172.4 (*C*=O), 183.7 (*C*=S); *m/z* (ESI$^+$) 522 (79, M+Na), 455 (100, M-Me$_2$N); HRMS $C_{21}H_{33}N_5O_5S_2Na^+$ calcd. 522.1821, found 522.1813.

(*S*)-2-(3-((1*R*,2*R*)-2-(4-Methoxyphenylsulfonamido)cyclohexyl)thioureido)-*N*,*N*,3,3-tetramethylbutanamide 268



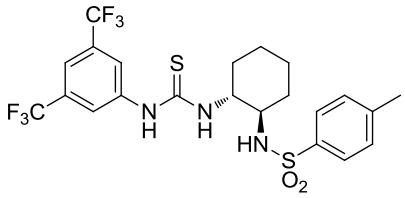
Prepared by General procedure J. Isothiocyanate **244** (0.63 mmol) gave, after purification by column chromatography (2.5% MeOH, 47.5% EtOAc, 50% CH_2Cl_2), **268** (273 mg, 0.56 mmol, 90% yield) as an off-white solid; mp 98-100 ^{o}C; $[\alpha]_D^{25}$ = +73.6 ^{o} (c = 0.990, $CHCl_3$); IR υ_{max} 3315 (C-H), 2938 (C-H), 1620 (C=O), 1531, 1319 (S=O), 1258 (C=S), 1154 (S=O), 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (9H, s, C(C*H*$_3$)$_3$), 1.04-1.13 (2H, m, *Cy*), 1.18-1.38 (2H, m, *Cy*), 1.63 (2H, t, *J* = 11.7, *Cy*), 1.95-2.13 (2H, m, *Cy*), 2.71-2.82 (1H, m, *Cy*), 2.85 (3H, s, N(*C*H$_3$)$_2$), 3.27 (3H, s, N(*C*H$_3$)$_2$), 3.85 (3H, s, OC*H*$_3$), 4.25-4.38 (1H, m, *Cy*), 5.76 (1H, d, *J* = 9.5, C*H*^{t}Bu), 6.73 (1H, d, *J* = 8.0, N*H*), 6.90 (2H, dm, *J* = 9.0, Ar*H*), 7.05 (2H, d, *J* = 9.3, N*H*), 7.64 (2H, d, *J* = 8.8, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 24.5 (*C*H$_2$), 24.8 (*C*H$_2$), 26.8 (C(*C*H$_3$)$_3$), 33.0 (*C*H$_2$), 34.0 (*C*H$_2$), 35.8 (N*C*H$_3$), 36.6 (*C*Me$_3$), 38.9 (N*C*H$_3$), 55.8 (O*C*H$_3$), 56.8 (*C*H), 59.0 (*C*H), 59.9 (*C*H), 114.2 (*Ar*H), 129.2 (*Ar*H), 132.6 (*Ar*), 162.7 (*Ar*O), 172.2 (*C*=O), 183.8 (*C*=S); *m/z* (ESI$^+$) 507 (88, M+Na), 440 (100, M-Me$_2$N); HRMS $C_{22}H_{36}N_4O_4S_2Na^+$ calcd. 507.2076, found 507.2066.

(*S*)-*N*,*N*,3,3-Tetramethyl-2-(3-((1*S*,2*S*)-2-(4-methylphenylsulfonamido)cyclohexyl)thioureido)butanamide 269



Prepared by General procedure J. Isothiocyanate **244** (0.68 mmol) gave crude **269** (445 mg) which was purified by column chromatography (2.5% MeOH, 47.5% EtOAc, 50% CH_2Cl_2) to give **269** (273 mg, 0.58 mmol, 86% yield) as an off-white solid; mp 181-183 ^oC; $[\alpha]_D^{25}$ = -75.7 ^{o} (c = 1.01, $CHCl_3$); IR υ_{max} 3305, 2931 (C-H), 1622 (C=O), 1539, 1326 (S=O), 1160 (S=O), 1074, 900, 666 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.90-1.09 (2H, m, *Cy*), 1.04 (9H, m, C(C*H*$_3$)$_3$), 1.14-1.33 (2H, m, *Cy*), 1.54-1.70 (2H, m, *Cy*), 1.80-1.97 (2H, m, *Cy*), 2.41 (3H, s, ArC*H*$_3$), 2.85-2.95 (4H, m, N(C*H*$_3$)$_2$, *Cy*), 3.26 (3H, s, N(C*H*$_3$)$_2$), 4.27 (1H, br. s, *Cy*), 5.60 (1H, br. s, C*H*^{t}Bu), 6.27-6.45 (1H, m, N*H*), 6.47-6.64 (1H, m, N*H*), 6.91-7.07 (1H, m, N*H*), 7.22-7.29 (2H, m, Ar*H*), 7.73 (2H, d, *J* = 8.3, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.7 (Ar*C*H$_3$), 24.6 (*C*H$_2$), 24.8 (*C*H$_2$), 26.9 (C(*C*H$_3$)), 32.7 (*C*H$_2$), 33.9 (*C*H$_2$), 35.9 (N*C*H$_3$), 36.1 (*C*Me$_3$) 38.8 (N*C*H$_3$), 56.3 (*C*H), 59.8 (*C*H), 60.2 (*C*H), 127.1 (*Ar*H), 129.6 (*Ar*H), 138.6 (*Ar*), 142.9 (*Ar*), 173.0 (*C*=O), 183.9 (*C*=S); *m/z* (CI) 469 (4, M+H), 435 (100, M-H_2O); HRMS $C_{22}H_{36}N_4O_3S_2H^+$ calcd. 469.2307, found 469.2305.

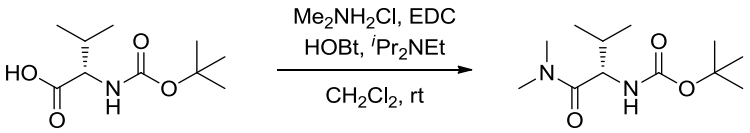
_N_-((1_R_,2_R_)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)cyclohexyl)-4-methylbenzenesulfonamide 270



Prepared by General procedure K. Isothiocyanate **244** (1.00 mmol) gave, after recrystallisation (CH_2Cl_2/pet. ether), **270** (384 mg, 0.71 mmol, 71% yield) as a white solid; mp 180-182 ^oC; $[\alpha]_D^{25}$ = +37.0 ^{o} (c = 1.03, $CHCl_3$); IR υ_{max} 3353, 3088 (C-H), 2935 (C-H), 2862 (C-H), 1538, 1387, 1305 (S=O), 1270 (C-F), 1113 (S=O) cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.13-1.23 (1H, m, *Cy*), 1.23-1.36 (3H, m, *Cy*), 1.64 (1H, apt. d, *J* = 13.4, *Cy*), 1.68-1.79 (2H, m, *Cy*), 2.13-2.22 (1H, m, *Cy*), 2.36 (3H, s, C*H*$_3$), 3.23 (1H, apt. td, *J* = 11.1, 4.0, *Cy*), 4.37 (1H, br. s, *Cy*), 6.28 (1H, br. s, N*H*), 6.88 (1H, d, *J* = 8.1, N*H*), 7.20-7.30 (2H, m, Ar*H*), 7.57 (1H, s, Ar*H*), 7.73 (2H, d, *J* = 8.3, Ar*H*), 7.91 (2H, s, Ar*H*), 8.48 (1H, br. s, N*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.5 (Ar*C*H$_3$), 24.5 (*C*H$_2$), 24.6 (*C*H$_2$), 32.1 (*C*H$_2$), 33.6 (*C*H$_2$), 57.4 (*C*H), 59.0 (*C*H), 118.7 (m, *Ar*H), 123.0 (2C, q, *J* = 272.9, *C*F$_3$), 123.7 (*Ar*H), 126.7 (*Ar*H), 129.9 (*Ar*H), 132.0 (2C, q, *J* = 33.0, *Ar*CF$_3$), 138.1 (*Ar*), 139.6 (*Ar*), 143.9 (*Ar*), 181.4

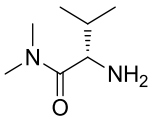
(*C*=S); *m/z* (ESI$^+$) 540 (100, M+H); HRMS $C_{22}H_{23}F_6N_3O_2S_2H^+$ calcd. 540.1214, found 540.1213.

(*S*)-*tert*-Butyl (1-(dimethylamino)-3-methyl-1-oxobutan-2-yl)carbamate



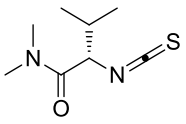
Prepared according to literature procedure.[174] *N*-Boc-*L*-valine (19.2 mmol) gave the title compound (4.60 g, 18.2 mmol, 95% yield). mp 54-55 ^oC; ^1H NMR (600 MHz, $CDCl_3$) δ 0.89 (3H, d, *J* = 6.8, CH(C*H*$_3$)$_2$), 0.94 (3H, d, *J* = 6.8, CH(C*H*$_3$)$_2$), 1.42 (9H, s, C(C*H*$_3$)$_3$), 1.87-1.97 (1H, m, C*H*Me$_2$), 2.96 (3H, s, N(*C*H$_3$)$_2$), 3.10 (3H, s, N(*C*H$_3$)$_2$), 4.46 (1H, dd, *J* = 9.2, 6.0, C*H*^{i}Pr), 5.37 (1H, d, *J* = 8.7, N*H*). ^1H NMR data are consistent with literature data.[167]

(*S*)-2-Amino-*N*,*N*,3-trimethylbutanamide



Prepared by General procedure G. (*S*)-*tert*-Butyl (1-(dimethylamino)-3-methyl-1-oxobutan-2-yl)carbamate (6.05 mmol) gave the title compound (820 mg, 5.70 mmol, 94% yield) as a white solid; mp 30-32 ^oC; ^1H NMR (600 MHz, $CDCl_3$) δ 0.91 (2H, d, *J* = 6.8, CH(C*H*$_3$)$_2$), 0.96 (2H, d, *J* = 7.0, CH(C*H*$_3$)$_2$), 1.70 (2H, br. s, N*H*$_2$), 1.85(1H, apt. oct, *J* = 6.6, C*H*Me$_2$), 2.97 (3H, s, N(*C*H$_3$)$_2$), 3.03 (3H, s, N(*C*H$_3$)$_2$), 3.50 (1H, d, *J* = 5.3, C*H*^{i}Pr). ^1H NMR data are consistent with literature data.[167]

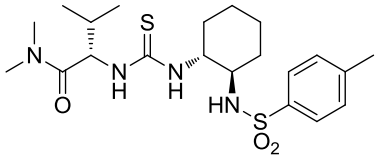
(*S*)-2-Isothiocyanato-*N*,*N*,3-trimethylbutanamide



Prepared by General procedure H. (*S*)-2-Amino-*N*,*N*,3-trimethylbutanamide (0.63 mmol) gave the title compound (107 mg, 0.58 mmol, 92% yield) as a colourless oil; IR υ_{max} 2967 (C-H), 2067 (N=C=S), 1655, 1495, 1400 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (3H, d, *J* = 6.8, CH(C*H*$_3$)$_2$), 1.06 (3H, d, *J* = 6.5, CH(C*H*$_3$)$_2$), 2.18-2.30 (1H, m, C*H*Me$_2$), 3.00 (3H, s, N(C*H*$_3$)$_2$), 3.06 (3H, s, N(C*H*$_3$)$_2$), 4.26 (1H, d, *J* = 5.8, C*H*^{i}Pr); ^{13}C NMR (151 MHz, $CDCl_3$) δ 17.8 (*C*H$_3$), 20.0 (*C*H$_3$), 32.2 (*C*H), 36.5

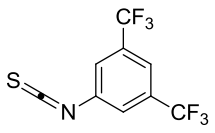
(NCH_3), 37.4 (NCH_3), 63.6 (*C*H), 136.6 (N=*C*=S), 166.9 (*C*=O); *m/z* (CI) 187 (75, M+H); HRMS $C_8H_{14}N_2OSH^+$ calcd. 187.0897, found 187.0950.

(*S*)-*N*,*N*,3-Trimethyl-2-(3-((1*R*,2*R*)-2-(4-methylphenylsulfonamido)cyclohexyl)thioureido)butanamide 271



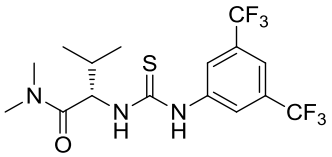
Prepared by General procedure J. (*S*)-2-Isothiocyanato-*N*,*N*,3-trimethylbutanamide (0.40 mmol) gave, after purification by column chromatography (2.5% MeOH, 47.5% EtOAc, 50% CH_2Cl_2), **271** (157 mg, 0.35 mmol, 86% yield) as an off-white solid; mp 75-77 ^oC; $[\alpha]_D^{25}$ = +39.8 ^{o} (c = 1.015, $CHCl_3$); IR υ_{max} 3303 (C-H), 2934 (C-H), 1625 (C=O), 1540, 1324 (S=O), 1159 (S=O/C=S), 1091 (C=S), 915, 730 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.91 (3H, dd, *J* = 6.8, 0.9, $CH(CH_3)_2$), 0.99 (3H, d, *J* = 6.8, $CH(CH_3)_2$), 1.02-1.16 (2H, m, *Cy*), 1.20-1.35 (2H, m, *Cy*), 1.56-1.70 (2H, m, *Cy*), 1.75-1.82 (1H, m, *Cy*), 1.95-2.09 (2H, m, *Cy*, $CHMe_2$), 2.38 (3H, s, $ArCH_3$), 2.86-2.93 (4H, m, *Cy*, $N(CH_3)_2$), 3.32 (3H, s, $N(CH_3)_2$), 4.31 (1H, m, *Cy*), 5.40-5.63 (1H, m, CH^iPr), 6.72-7.03 (2H, br. m, N*H*), 7.20 (2H, d, *J* = 7.3, Ar*H*), 7.52-7.63 (1H, br. m, N*H*), 7.65 (2H, d, *J* = 7.9, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.6 ($C(CH_3)_2$), 18.9 ($C(CH_3)_2$), 21.7 ($ArCH_3$), 24.4 (CH_2), 24.8 (CH_2), 33.0 (CH_2), 33.0 ($CHMe_2$), 33.8 (CH_2), 36.0 (NCH_3), 38.5 (NCH_3), 56.2 (*C*H), 58.9 (C*H*), 59.8 (*C*H), 126.9 (*Ar*H), 129.5 (*Ar*H), 138.5 (*Ar*), 143.1 (*Ar*), 173.1 (*C*=O), 183.7 (*C*=S); *m/z* (ESI^+) 477 (57, M+Na), 410 (100, M-Me_2N); HRMS $C_{21}H_{34}N_4O_3S_2Na^+$ calcd. 477.1970, found 477.1961.

1-Isothiocyanato-3,5-bis(trifluoromethyl)benzene



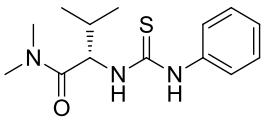
Prepared by General procedure H. 3,5-Bis(trifluoromethyl)aniline (21.8 mmol) gave the title compound (5.33 g, 19.7 mmol, 90% yield) as a pale yellow oil; ^1H NMR (600 MHz, $CDCl_3$) δ 7.64 (2H, s, Ar*H*), 7.76 (1H, s, Ar*H*). ^1H NMR data are consistent with literature data.[175]

(*S*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-*N*,*N*,3-trimethylbutanamide 272



Prepared by General procedure K. 1-Isothiocyanato-3,5-bis(trifluoromethyl) benzene (5.18 mmol) gave crude **272** (2.03 g) which was recrystallised (40% TBME/pet. ether) to give **272** (1.62 g, 3.90 mmol, 75% yield) as a white solid; mp 135-136 ^{o}C; $[\alpha]_D^{25}$ = -45.9 ^{o} (c = 1.015, $CHCl_3$); IR υ_{max} 3320 (C-H), 2971 (C-H), 1609 (C=O), 1534, 1380, 1272, 1164, 1111 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.05 (3H, d, *J* = 6.8, CH(C*H*$_3$)$_2$), 1.10 (3H, d, *J* = 6.8, CH(C*H*$_3$)$_2$), 2.06 (1H, apt. oct, *J* = 7.0, C*H*(CH$_3$)$_2$), 3.05 (3H, s, N(C*H*$_3$)$_2$), 3.39 (3H, s, N(C*H*$_3$)$_2$), 5.34 (1H, apt. t, *J* = 8.2, C*H*^{i}Pr), 7.51 (1H, s, Ar*H*), 8.04 (2H, s, Ar*H*), 8.30 (1H, d, *J* = 7.7, N*H*), 9.43 (1H, br. s, ArN*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 19.1 (C(*C*H$_3$)$_2$), 19.2 (C(*C*H$_3$)$_2$), 32.0 (*C*Me$_2$), 36.3 (N*C*H$_3$), 38.5 (N*C*H$_3$), 59.3 (*C*H^{i}Pr), 117.6 (1C, m, Ar*H*), 122.6 (2C, m, Ar*H*), 123.3 (2C, q, *J* = 272.9, *C*F$_3$), 131.5 (2C, q, *J* = 34.1, *Ar*CF$_3$), 140.7 (*Ar*), 174.6 (*C*=O), 181.5 (*C*=S); *m/z* (CI) 416 (18, M+H), 396 (34, M-F), 371 (100, M–Me$_2$N); HRMS $C_{16}H_{19}F_6N_3OSH^+$ calcd. 416.12313, found 416.12264.

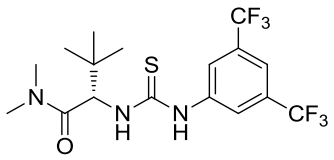
(*S*)-*N*,*N*,3-Trimethyl-2-(3-phenylthioureido)butanamide 279



Prepared by General procedure K. Phenyl isothiocyanate (0.67 mmol) gave, after purification by column chromatography (20% EtOAc/CH_2Cl_2), **279** (139 mg, 0.50 mmol, 74% yield) as a white solid; mp 133-135 ^{o}C; $[\alpha]_D^{25}$ = +39.2 ^{o} (c = 1.06, $CHCl_3$); IR υ_{max} 3311 (C-H), 2965 (C-H), 1628 (C=O), 1596, 1538, 1495, 1308 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.94 (3H, d, *J* = 6.8, CH(C*H*$_3$)$_2$), 1.00 (3H, d, *J* = 6.8, CH(C*H*$_3$)$_2$), 2.04 (1H, apt. oct, *J* = 6.8, C*H*Me$_2$), 2.94 (3H, s, N(C*H*$_3$)$_2$), 3.23 (3H, s, N(C*H*$_3$)$_2$), 5.51 (1H, apt. t, *J* = 7.8, C*H*^{i}Pr), 7.18 (1H, br. s, *NH*) *7*.22-7.26 (1H, m, Ar*H*), 7.29 (2H, d, *J* = 7.7, Ar*H*), 7.36-7.43 (2H, m, Ar*H*), 8.17 (1H, br. m, N*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.4 (C(*C*H$_3$)$_2$), 19.4 (C(*C*H$_3$)$_2$), 32.2 (*C*HMe$_2$), 35.9 (N*C*H$_3$), 37.9 (N*C*H$_3$), 59.6 (*C*H^{i}Pr), 125.0 (*Ar*H), 126.9 (*Ar*H), 129.9 (*Ar*H), 136.7

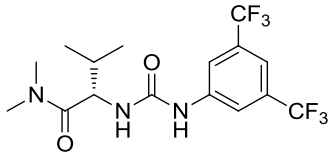
(*Ar*), 172.4 (*C*=O), 180.9 (*C*=S); *m/z* (EI) 279 (5, M), 234 (100, M-Me_2NH_2); HRMS $C_{14}H_{21}N_3O_S$ calcd. 279.1405, found 279.1396.

(*S*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-*N*,*N*,3,3-tetramethylbutanamide 280



Prepared by General procedure K. 1-Isothiocyanato-3,5-bis(trifluoromethyl) benzene (0.52 mmol) gave, after purification by column chromatography (5% MeOH/CH_2Cl_2), **280** (178 mg, 0.41 mmol, 80% yield) as a white solid; mp 112-114 ^oC; $[\alpha]_D^{25}$ = -32.4 ^{o} (c = 1.01, $CHCl_3$); IR υ_{max} 3328 (C-H), 2968 (C-H), 1615 (C=O), 1533, 1474, 1385, 1277, 1176, 1132 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.12 (9H, s, C(CH_3)$_3$), 2.96 (3H, s, N(CH_3)$_2$), 3.34 (3H, s, N(CH_3)$_2$), 5.66 (1H, d, *J* = 9.2, C*H*^{t}Bu), 7.55 (1H, s, Ar*H*), 7.79 (1H, d, *J* = 9.0, N*H*), 7.90 (2H, s, Ar*H*), 9.11 (1H, s, N*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.2 (C(*C*H$_3$)$_3$), 36.0 (*C*Me$_3$), 36.2 (N*C*H$_3$), 39.0 (N*C*H$_3$), 60.8 (*C*H^{t}Bu), 118.2 (1C, dq, *J* = 3.3, 3.3, *Ar*H), 123.2 (2C, q, *J* = 279.2, *C*F$_3$), 123.7 (2C, m, *Ar*H), 131.7 (2C, q, *J* = 34.1, *Ar*CF$_3$), 140.2 (*Ar*), 173.8 (*C*=O), 181.8 (*C*=S); *m/z* (CI) 430 (45, M+H), 410 (63, M-F), 385 (67, M-NMe_2); HRMS $C_{17}H_{21}F_6N_3OSH^+$ calcd. 430.1388, found 430.1383.

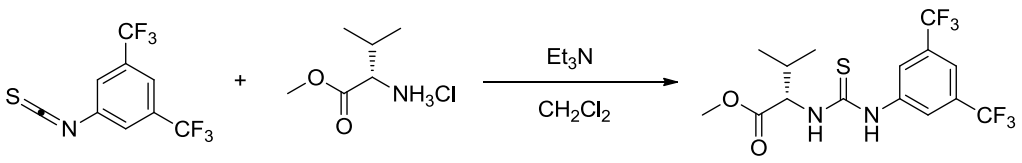
(*S*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)-*N*,*N*,3-trimethylbutanamide 281



Prepared by General procedure K. 3,5-Bis(trifluoromethyl)phenyl isocyanate (0.42 mmol) afforded, after recrystallisation (25% TBME/pet. ether), **281** (90 mg, 0.23 mmol, 54% yield) as a white solid; mp 162-164 ^oC; $[\alpha]_D^{25}$ = -25.7 ^{o} (c = 1.02, $CHCl_3$); IR υ_{max} 3343, 3116, 2968 (C-H), 1704 (C=O), 1611, 1287, 1117 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.05 (6H, dd, *J* = 6.8, 2.3, CH(CH_3)$_2$), 1.96-2.05 (1H, m, C*H*Me$_2$), 3.12 (3H, s, N(CH_3)$_2$), 3.32 (3H, s, N(CH_3)$_2$), 4.75 (1H, apt. t, *J* = 8.2, C*H*^{i}Pr), 6.84 (1H, d, *J* = 9.0, N*H*), 7.34 (1H, s, Ar*H*), 7.72 (2H, s, Ar*H*), 8.53 (1H, s,

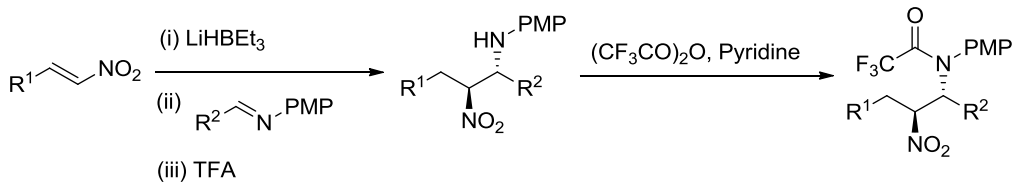
N*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.4 (C(*C*H_3)$_2$), 19.6 (C(*C*H_3)$_2$), 31.6 (*C*HMe$_2$), 36.3 (N*C*H_3), 38.2 (N*C*H_3), 54.9 (*C*H^{i}Pr), 115.1 (1C, m, *Ar*H), 117.9 (2C, m, *Ar*H), 123.4 (2C, q, *J* = 272.9, *C*F_3), 131.8 (2C, q, *J* = 33.0, *Ar*CF_3), 141.1 (*Ar*N), 155.3 (*C*=O), 174.9 (*C*=O); *m/z* (CI) 400 (23, M+H), 380 (100, M-F), 355 (22, M-NMe$_2$), 327 (96, M-Me$_2$NCO); HRMS $C_{16}H_{19}F_6N_3O_2H^+$ calcd. 400.1460, found 400.1442.

(*S*)-Methyl 2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-3-methylbutanoate 282



To a mixture of 1-Isothiocyanato-3,5-bis(trifluoromethyl)benzene (406 mg, 1.50 mmol) and *L*-valine methyl ester hydrochloride (335 mg, 2.00 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (210 μL, 1.50 mmol) and the reaction was stirred at room temperature until reaction complete as judged by tlc analysis (*ca.* 24 h). The excess solvent was then removed to give crude **282** which was purified by column chromatography (25% EtOAc/pet. ether) to give **282** (450 mg, 1.12 mmol, 75% yield) as a colourless oil; $[\alpha]_D^{25}$ = +17.1 ^{o} (c = 1.005, $CHCl_3$); IR υ_{max} 3309, 2968 (C-H), 1716 (C=O), 1535, 1473, 1383, 1278, 1177, 1132; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.98 (3H, d, *J* = 7.0, CH(C*H*$_3$)$_2$), 1.02 (3H, d, *J* = 7.0, CH(C*H*$_3$)$_2$), 2.25-2.35 (1H, m, C*H*Me$_2$), 3.80 (3H, s, OC*H*$_3$), 5.17 (1H, br. s, C*H*^{i}Pr), 7.34 (1H, d, *J* = 8.8, N*H*), 7.63 (1H, s, Ar*H*), 7.94 (2H, s, Ar*H*), 8.81 (1H, s, N*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.7 (C(*C*H_3)$_2$), 19.0 (C(*C*H_3)$_2$), 31.3 (*C*HMe$_2$), 52.9 (O*C*H_3), 62.9 (*C*H^{i}Pr), 119.0 (1C, m, *Ar*H), 122.9 (2C, q, *J* = 273.1, *C*F_3), 123.4 (2C, m, *Ar*H), 132.5 (2C, q, *J* = 31.3, *Ar*CF_3), 139.3 (*Ar*), 174.4 (*C*=O), 181.5 (*C*=S); *m/z* (CI) 403 (100, M+H); HRMS $C_{15}H_{16}F_6N_2O_2SH^+$ calcd. 403.0915, found 403.0904.

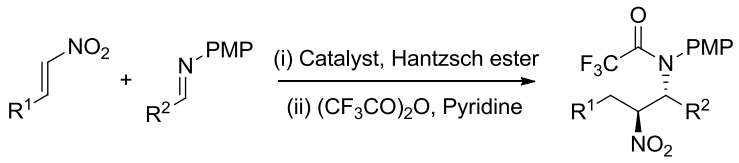
4.2.4 Preparation of *β*-nitroamines and *β*-nitrotrifluoroacetamides



General Procedure L: To a solution of nitroalkene **84** (limiting reagent) in THF (6 mL per mmol) was added Superhydride^{TM} (1.1 equiv., 1.0 M in THF). The

suspension was then stirred for 30 min at rt before cooling to –78 °C over 30 min. A solution of imine **30** (1.1 equiv.) in THF (6 mL per mmol) was added *via* cannula and the mixture stirred at -78 °C for 10 min. A solution of TFA (2.5 equiv.) in THF (2 mL per mmol) was then added by cannula and the reaction stirred for 1 h at –78 °C. The reaction was then quenched with sat. aq. NH_4Cl (10 mL per mmol) and diluted with Et_2O (20 mL per mmol). The organic phase was washed with sat. brine (10 mL per mmol) and dried ($MgSO_4$). The excess solvents were then removed *in vacuo* to afford crude *β*-nitroamine. Crude *β*-nitroamine was re-dissolved in CH_2Cl_2 (5 mL per mmol) and trifluoroacetic anhydride (5.0 equiv.), followed by pyridine (5.0 equiv.) were added at rt and the solution was stirred at rt for 2 h. After this time, 2.0 M HCl (10 mL per mmol) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL per mmol) and the combined organic phases were washed with sat. aq. $NaHCO_3$ (10 mL per mmol) and sat. brine (10 mL per mmol). The organic phase was then dried ($MgSO_4$) and the excess solvents were removed *in vacuo* to afford crude *β*-nitrotrifluoroacetamide.

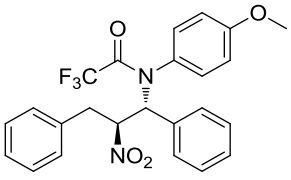
General Procedure M: To a solution of nitroalkene **84** (limiting reagent) in CH_2Cl_2 (6 mL per mmol) was added Superhydride^{TM} (1.1 equiv., 1.0 M in THF). The suspension was then stirred for 30 min at rt before cooling to –78 °C over 30 min. A solution of imine **30** (1.1 equiv.) in CH_2Cl_2 (6 mL per mmol) was then added *via* cannula and the mixture stirred at -78 °C for 10 min. A solution of TFA (1.2 equiv.) was added and the reaction was stirred for 1 h at –78 °C. The reaction was then quenched with sat. aq. NH_4Cl (10 mL per mmol) and diluted with Et_2O (20 mL per mmol). The organic phase was washed with sat. brine (10 mL per mmol) and dried ($MgSO_4$). The excess solvents were then removed *in vacuo* to afford crude *β*-nitroamine. Crude *β*-nitroamine was re-dissolved in CH_2Cl_2 (5 mL per mmol) and trifluoroacetic anhydride (5.0 equiv.), followed by pyridine (5.0 equiv.) were added at rt and the solution was stirred at rt for 2 h. After this time, 2.0 M HCl (10 mL per mmol) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL per mmol) and the combined organic phases were washed with sat. aq. $NaHCO_3$ (10 mL per mmol) and sat. brine (10 mL per mmol). The organic phase was then dried ($MgSO_4$) and the excess solvents were removed *in vacuo* to afford crude *β*-nitrotrifluoroacetamide.



General Procedure N: For catalyst screening. To a flask containing *N*-PMP-phenyl imine **30a** (0.20 mmol), *β*-nitrostyrene **84a** (0.40 mmol), Hantzsch ester **254** (0.40 mmol) and catalyst (0.02 mmol) was added toluene (1.5 mL) and the reaction was stirred at room temperature for 2 h. After this time, a small aliquot (10 μL) was removed and analysed by ^{1}H NMR spectroscopy to measure reaction progress. Then trifluoroacetic anhydride (1.0 mmol), followed by pyridine (1.0 mmol) were added at -20 ^{o}C and the solution was allowed to warm to rt and stirred for 2 h. After this time, 2.0 M HCl (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic phases were washed with sat. aq. $NaHCO_3$ 10 mL) and sat. brine (10 mL). The organic phase was then dried ($MgSO_4$) and the excess solvents were removed *in vacuo* to afford crude *β*-nitrotrifluoroacetamide.

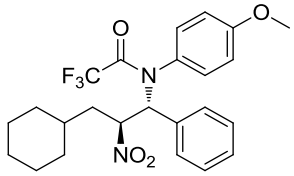
General Procedure O: For asymmetric reactions at -20 ^{o}C. To a mixture containing imine (limiting reagent), nitroalkene (2.0 equiv.) and Hantzsch ester **254** (2.0 equiv.) in toluene (1.5 mL per mmol) cooled to -20 ^{o}C (Cryobath) was added a solution of catalyst (0.1 equiv., 0.2 M in toluene) and the reaction was stirred until reaction complete as monitored by ^{1}H NMR. Once reaction complete, trifluoroacetic anhydride (5.0 equiv.), followed by pyridine (5.0 equiv.) were added at -20 ^{o}C and the solution was allowed to warm to rt and stirred for 2 h. After this time, 2.0 M HCl (10.0 mL per mmol) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL per mmol) and the combined organic phases were washed with sat. aq. $NaHCO_3$ (10 mL per mmol) and sat. brine (10 mL per mmol). The organic phase was then dried ($MgSO_4$) and the excess solvents were removed *in vacuo* to afford crude *β*-nitrotrifluoroacetamide.

2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R*,2*S*)-2-nitro-1,3-diphenylpropyl)acetamide 239aa



When prepared by general procedure L. Nitroalkene **84a** (0.50 mmol) afforded, after purification by column chromatography (10% EtOAc/pet. ether), **239aa** (188 mg, 0.41 mmol, 82% yield) as a yellow solid; mp 128-131 ^{o}C; IR υ_{max} 2936 (C-H), 1699 (C=O), 1557 (N-O), 1511, 1254, 1209, 1169 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.47 (1H, dd, *J* = 14.4, 10.8, PhC*H*$_2$), 3.56 (1H, dd, *J* = 14.4, 3.0, PhC*H*$_2$), 3.83 (3H, s, OC*H*$_3$), 5.61 (1H, br. s, C*H*NO_2), 6.06 (1H, br. s, C*H*N), 6.39 (1H, br. s, Ar*H*), 6.72 (1H, dd, *J* = 8.4, 2.4, Ar*H*), 6.93 (1H, dd, *J* = 8.4, 2.4, Ar*H*), 7.04 (1H, br. d, *J* = 7.8, Ar*H*), 7.12 (2H, d, *J* = 7.2, Ar*H*), 7.22-7.27 (3H, m, Ar*H*), 7.29-7.38 (5H, m, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ-67.8 (3F, s, C*F*$_3$); ^{13}C NMR (151 MHz, CDCl3) δ 38.4 (Ph*C*H$_2$), 55.7 (O*C*H$_3$), 65.2 (Ph*C*HN), 89.8 (*C*HNO_2), 114.1 (*Ar*H), 114.5 (*Ar*H), 116.3 (1C, q, *J* = 286.5, *C*F$_3$), 128.0 (*Ar*H), 128.7 (*Ar*H), 128.9 (*Ar*H), 129.2 (*Ar*H), 129.4 (*Ar*H), 129.9 (*Ar*H), 130.2 (*Ar*H) 132.2 (*Ar*H), 133.2 (*Ar*), 134.6 (*Ar*), 158.3 (1C, q, *J* = 36.0, *C*=O), 160.1 (*Ar*O); *m/z* (EI) 458 (17, M), 219 (96, M+H–$C_{15}H_{14}NO_2$); HRMS $C_{24}H_{21}F_3N_2O_4$ calcd. 458.1448, found 458.1456; anal. calcd. for $C_{24}H_{21}F_3N_2O_4$ C, 62.88; H, 4.62; N, 6.11. Found. C, 62.47; H, 4.49; N, 6.06%. **When prepared by general procedure O**. Imine **30a** (0.200 mmol) afforded, after purification by column chromatography (10% Me_2CO/pet. ether and 50% CH_2Cl_2/pet. ether), **239aa** (74 mg, 0.162 mmol, 81 % yield) as a yellow foamy solid; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 95:5, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 7.8 min, t_r (minor) = 10.6 min, shows 98% *ee*; mp 70-72 ^{o}C; $[\alpha]_D^{25}$ = -61.5 ^{o} (c = 1.01, $CHCl_3$).

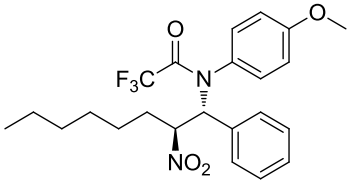
_N_-((1_R_,2_S_)-3-Cyclohexyl-2-nitro-1-phenylpropyl)-2,2,2-trifluoro-_N_-(4-methoxyphenyl)acetamide 239ba



When prepared by general procedure L. Nitroalkene **84b** (0.50 mmol) afforded, after purification by column chromatography (4% Me_2CO/pet. ether), **239ba** (405 mg, 0.87 mmol, 87% yield) as a white solid; mp 164-167 ^{o}C; IR υ_{max} 2927 (C-H), 1701 (C=O), 1555 (N-O), 1511, 1256, 1209, 1156 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.01(1H, apt. qd, *J* = 12.0, 3.0, *Cy*), 1.08 (1H, apt qd, *J* = 12.0, 3.0, *Cy*), 1.25 (4H, m, Cy), 1.70 (3H, m, *Cy*), 1.80 (1H, br. d, *J* = 13.2, *Cy*), 1.90 (1H, m, CyC*H*$_2$), 2.09

(1H, br. d, *J* = 12.0, *Cy*), 2.28 (1H, m, CyC*H*$_2$), 3.82 (3H, s, OC*H*$_3$), 5.45 (1H, br. s, C*H*NO$_2$), 6.03 (1H, br. s, C*H*N), 6.24 (1H, br. s, Ar*H*), 6.66 (1H, br. d, *J* = 10.2, Ar*H*), 6.89 (1H, dd, *J* = 9.0, 3.0, Ar*H*), 6.96 (1H, br. d, *J* = 7.8, Ar*H*), 7.06 (2H, d, *J* = 7.8, Ar*H*), 7.24 (2H, t, *J* = 7.8, Ar*H*), 7.31 (1H, t, *J* = 7.8, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -67.6 (3F, s, C*F*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 26.0 (*C*H$_2$), 26.2 (*C*H$_2$), 26.3 (*C*H$_2$), 31.9 (*C*H$_2$), 34.1 (*C*H$_2$), 34.5 (*C*H), 39.5 (Cy*C*H$_2$), 55.6 (O*C*H$_3$), 64.3 (*C*HN), 85.6 (*C*HNO$_2$), 113.9 (*Ar*H), 114.3 (*Ar*H), 116.3 (1C, q, *J* = 288.7, *C*F$_3$), 127.6 (br., *Ar*) 128.8 (*Ar*H), 129.3 (*Ar*H), 129.7 (*Ar*H), 130.2 (*Ar*H), 132.5 (br., *Ar*H), 133.4 (*Ar*), 158.0 (1C, q, *J* = 35.9, *C*=O), 160.47 (*Ar*O); *m/z* (EI) 464 (38, M); HRMS $C_{24}H_{27}F_3N_2O_4$ calcd. 464.1917, found 464.1905; anal. calcd. for $C_{24}H_{27}F_3N_2O_4$: C, 62.06; H, 5.86; N, 6.03; found C, 61.89; H, 5.84; N, 5.97%. **When prepared by general procedure O**. Imine **30a** (0.200 mmol) afforded, after purification by column chromatography (4% Me_2CO/pet. ether and 40% CH_2Cl_2/pet. ether), **239aa** (70 mg, 0.150 mmol, 75% yield) as a yellow foam; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 95:5, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 4.8 min, t_r (minor) = 6.2 min, shows 95% *ee*; mp 56-57 ^{o}C; $[\alpha]_D^{25}$ = -38.7 ^{o} (c = 1.00, $CHCl_3$).

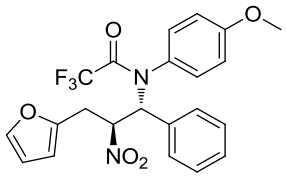
2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R*,2*S*)-2-nitro-1-phenyloctyl) acetamide 239ca



When prepared by general procedure L. Nitroalkene **84c** (0.50 mmol) afforded, after purification by column chromatography (7.5% Me_2CO/pet. ether), **239ca** (184 mg, 0.41 mmol, 82% yield) as a yellow oil; IR υ_{max} 2931 (C-H), 1698 (C=O), 1554 (N-O), 1510, 1254, 1206, 1180, 1152 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 6.6, C*H*$_3$CH$_2$), 1.30-1.50 (8H, m, Me(C*H*$_2$)$_4$CH$_2$), 2.14 (1H, m, ^{n}PnC*H*$_2$), 2.26 (1H, m, ^{n}PnC*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 5.30 (1H, br. s, C*H*NO$_2$), 6.03 (1H, br. s, C*H*N), 6.27 (1H, br. s, Ar*H*), 6.66 (1H, d, *J* = 9.0, Ar*H*), 6.88 (1H, dd, *J* = 9.0, 3.0, Ar*H*), 6.92 (1H, d, *J* = 8.4, Ar*H*), 7.07 (2H, d, *J* = 7.8, Ar*H*), 7.24 (2H, d, *J* = 7.8, Ar*H*), 7.31 (1H, t, *J* = 7.2, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ-67.51 (3F, s, C*F*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.1 (*C*H$_3$CH$_2$), 22.6 (Me*C*H$_2$), 25.9 (*C*H$_2$), 28.6

(CH_2), 31.6 (CH_2), 32.0 (CH_2), 55.6 (OCH_3), 64.3 (*C*HN), 88.0 (*C*HNO_2), 114.0 (*Ar*H), 114.3 (*Ar*H), 116.3 (1C, q, *J* = 289.3, *C*F_3), 127.7 (*Ar*), 128.8 (*Ar*H), 129.2 (*Ar*H), 129.7 (*Ar*H), 130.1 (*Ar*H), 132.4 (*Ar*H), 133.5 (*Ar*), 158.0 (1C, q, *J* = 34.4, *C*=O), 160.5 (*Ar*O); *m/z* 452 (32, M); HRMS $C_{23}H_{27}F_3N_2O_4$ calcd. 452.19174, found 452.19160. **When prepared by general procedure O**. Imine **30a** (0.200 mmol) afforded, after purification by column chromatography (7.5% Me_2CO/pet. ether and 40% CH_2Cl_2/pet. ether), **239ca** (64 mg, 0.142 mmol, 71% yield) as a yellow oil; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 99:1, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 7.9 min, t_r (minor) = 9.3 min, shows 97% *ee*; $[\alpha]_D^{25}$ = -12.9 ^{o} (c = 0.96, $CHCl_3$).

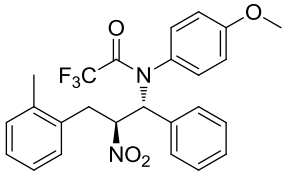
2,2,2-Trifluoro-*N*-((1*S,2*R**)-3-(furan-2-yl)-2-nitro-1-phenylpropyl)-*N*-(4-methoxyphenyl)acetamide 239da**



When prepared by general procedure L. Nitroalkene **84d** (70 mg, 0.50 mmol) afforded after purification by column chromatography (10% EtOAc/pet. ether) *β*-nitrotrifluoroacetamide **239da** (176 mg, 0.39 mmol, 79% yield) as a yellow solid; mp 118-121 ^oC; IR υ_{max} 2939 (C-H), 1699 (C=O), 1558 (N-O), 1511, 1255, 1208, 1182, 1156 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.57 (1H, dd, *J* = 16.2, 3.6, PhCH_2), 3.63 (1H, dd, *J* = 16.2, 10.2, PhCH_2), 3.83 (3H, s, OCH_3), 5.24, (1H, br. t, *J* = 10.2, C*H*NO_2), 6.17 (1H, d, *J* = 7.8, Ar*H*), 6.21 (1H, d, *J* = 3.0, Ar*H*), 6.32 (1H, br. s, C*H*N), 6.34 (1H, dd, *J* = 3.0, 1.8, Ar*H*), 6.64 (1H, dd, *J* = 9.0, 3.0, Ar*H*), 6.97 (1H, dd, *J* = 8.4, 2.4, Ar*H*), 7.04 (2H, d, *J* = 7.2, Ar*H*), 7.15 (1H, dd, *J* = 8.4, 2.4, Ar*H*), 7.24 (2H, t, *J* = 7.8, Ar*H*), 7.33 (1H, m, Ar*H*), 7.44 (1H, d, *J* = 1.2, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -67.5 (3F, s, CF_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 31.2 (Ph*C*H_2), 55.6 (OCH_3), 62.8 (*C*HN), 86.6 (*C*HNO_2), 108.9 (*Ar*H), 110.9 (*Ar*H), 114.1 (*Ar*H), 114.2 (*Ar*H), 116.3 (1C, q, *J* = 288.4, *C*F_3), 127.8 (*Ar*), 128.8 (*Ar*H), 129.3 (*Ar*H), 129.9 (*Ar*H), 130.4 (*Ar*H), 132.7 (*Ar*), 132.9 (*Ar*H), 142.9 (*Ar*H), 148.2 (*Ar*), 158.3 (1C, q, *J* = 36.2, *C*=O), 160.6 (*Ar*O); *m/z* (CI) 449 **(**3, M+H**)**, 402 (88, M–NO_2); HRMS $C_{22}H_{19}F_3N_2O_5H^+$ calcd. 449.1324, found 449.1310; anal. calcd. for $C_{22}H_{19}F_3N_2O_5$: C, 58.93; H, 4.27; N, 6.25; found C, 58.74; H, 4.21; N, 6.20. **When**

prepared by general procedure O. Imine **30a** (0.200 mmol) afforded, after purification by column chromatography (4% Me_2CO/pet. ether and 40% CH_2Cl_2/pet. ether), **239da** (29 mg, 0.064 mmol, 32 % yield) as a yellow foam; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 95:5, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 8.8 min, t_r (minor) = 14.8 min, shows 95% *ee*; $[\alpha]_D^{25}$ = -66.2 ^{o} (c = 0.75, $CHCl_3$).

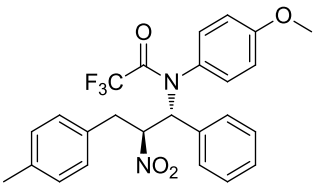
2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S*,2*R*)-2-nitro-1-phenyl-3-(*o*-tolyl)propyl)acetamide 239ea



When prepared by general procedure L. Nitroalkene **84e** (82 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me_2CO/pet. ether) *β*-nitrotrifluoroacetamide **239ea** (170 mg, 0.36 mmol, 72% yield) as an off-white solid; mp 143-145 ^oC; IR υ_{max} 2937 (C-H), 1699 (C=O), 1558 (N-O), 1511, 1254, 1210, 1168 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.41 (3H, s, ArCH_3), 3.54 (2H, m, ArCH_2), 3.84 (3H, s, OCH_3), 5.82 (2H, m, C*H*NO_2C*H*N), 6.57 (1H, br. s, Ar*H*), 6.77 (1H, d, *J* = 7.2, Ar*H*), 6.89 (1H, dd, *J* = 8.4, 2.4, Ar*H*), 6.98 (1H, d, *J* = 8.4, Ar*H*), 7.14-7.21 (6H, m, Ar*H*), 7.27 (2H, t, *J* = 7.8, Ar*H*), 7.34 (1H, m, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -67.8 (3F, s, CF_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 19.7 (Ar*C*H_3), 35.5 (Ar*C*H_2), 55.7 (O*C*H_3), 67.3 (*C*HN), 88.4 (*C*HNO_2), 114.1 (*Ar*H), 114.7 (*Ar*H), 116.3 (1C, q, *J* = 288.7, *C*F_3), 126.7 (*Ar*H), 128.0 (*Ar*H), 129.0 (*Ar*H), 129.3 (*Ar*H), 129.5 (*Ar*H), 129.8 (*Ar*H), 130.3 (*Ar*H), 131.0 (*Ar*H), 131.6 (*Ar*H), 132.6 (*Ar*), 133.4 (*Ar)*, 136.6 (*Ar*), 158.1 (1C, q, *J* = 35.6, *C*=O), 160.5 (*Ar*O); *m/z* (EI) 472 **(**4, M**)**, 219 (77, M+H-$C_{16}H_{16}NO_2$); HRMS $C_{25}H_{23}F_3N_2O_4$ calcd. 472.1604, found 472.1606; anal. calcd. for $C_{25}H_{23}F_3N_2O_4$: C, 63.55; H, 4.91; N, 5.93; found C, 63.26; H, 4.81; N, 5.86. **When prepared by general procedure O**. Imine 30a (0.200 mmol) afforded, after purification by column chromatography (4% Me_2CO/pet. ether and 40% CH_2Cl_2/pet. ether), **239ea** (66 mg, 0.140 mmol, 70% yield) as a yellow foamy solid; mp 52-54 ^oC; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 99:1, flow rate = 1 mL/min, λ = 254 nm): retention time t_r

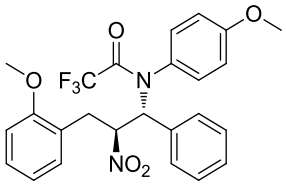
(major) = 10.0 min, t_r (minor) = 12.3 min, shows 98% *ee*; $[\alpha]_D^{25}$ = -74.9 ^{o} (c = 1.03, $CHCl_3$).

2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S,2*R**)-2-nitro-1-phenyl-3-(*p*-tolyl)propyl)acetamide 239fa**



When prepared by general procedure L. Nitroalkene **84f** (82 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me_2CO/pet. ether) *β*-nitrotrifluoroacetamide **239fa** (176 mg, 0.37 mmol, 75% yield) as a yellow solid; mp 92-96 ^{o}C; IR υ_{max} 2932 (C-H), 1699 (C=O), 1557 (N-O), 1511, 1255, 1209, 1168 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.33 (3H, s, ArC*H*$_3$), 3.43 (1H, dd, *J* = 14.4, 10.8, PhC*H*$_2$), 3.51 (1H, dd, *J* = 14.4, 3.0, PhC*H*$_2$), 3.83 (3H, s, OC*H*$_3$), 5.57 (1H, br. s, C*H*NO_2), 6.06 (1H, br. s, C*H*N), 6.38 (1H, br. s, Ar*H*), 6.71 (1H, dd, *J* = 8.4, 2.4, Ar*H*), 6.93 (1H, dd, *J* = 9.0, 3.0, Ar*H*), 7.05 (1H, d, *J* = 8.4, Ar*H*), 7.10-7.13 (4H, m, Ar*H*), 7.15 (2H, d, *J* = 7.8, Ar*H*), 7.25 (2H, t, *J* = 7.8, Ar*H*), 7.33 (1H, m, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ-67.6 (3F, s, C*F*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.2 (Ar*C*H_3), 38.0 (Ar*C*H_2), 55.6 (O*C*H_3), 65.2 (*C*HN), 89.8 (*C*HNO_2), 114.1 (*Ar*H), 114.5 (*Ar*H), 116.3 (1C, q, *J* = 289.0, *C*F_3), 128.0 (*Ar*), 128.6 (*Ar*H), 128.9 (*Ar*H), 129.4 (*Ar*H), 129.7 (*Ar*H), 129.9 (*Ar*H), 130.2 (*Ar*H) 131.5 (*Ar*), 132.2 (*Ar*H), 133.2 (*Ar*), 137.7 (*Ar*), 158.1 (1C, q, *J* = 35.9, *C*=O), 160.5 (*Ar*O); *m/z* (EI) 472 **(**3, M**)**, 219 (40, M+H-$C_{16}H_{16}NO_2$); HRMS $C_{25}H_{23}F_3N_2O_4$ calcd. 472.1604, found 472.1606; anal. calcd. for $C_{25}H_{23}F_3N_2O_4$: C, 63.55; H, 4.91; N, 5.93; found C, 63.24; H, 4.92; N, 5.80.

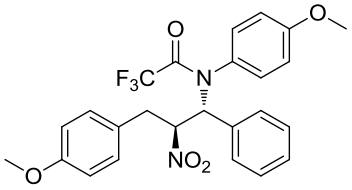
2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R*,2*S*)-3-(2-methoxyphenyl)-2-nitro-1-phenylpropyl)acetamide 239ga



When prepared by general procedure L. Nitroalkene **84g** (0.50 mmol) afforded, after purification by column chromatography (10% EtOAc/pet. ether), **239ga** (192

mg, 0.39 mmol, 79% yield) as a yellow solid; mp 146-150 ^{o}C; IR υ_{max} 2938 (C-H), 1698 (C=O), 1556 (N-O) 1513 (C=C), 1496, 1248, 1208, 1155 (N-O) cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.31 (1H, dd, *J* = 14.4, 12.0, ArC*H*$_2$), 3.78 (1H, dd, *J* = 14.4, 3, ArC*H*$_2$), 3.82 (3H, s, OC*H*$_3$), 4.00 (3H, s, OC*H*$_3$), 5.54 (1H, br. t, *J* = 9.6, C*H*NO_2), 6.08 (1H, br. d, *J* = 7.2, C*H*N), 6.52 (1H br. d, *J* = 8.4, Ar*H*), 6.57 (1H, dd, *J* = 8.4, 2.4, Ar*H*), 6.89 (1H, td, *J* = 7.8, 0.6, Ar*H*), 6.93 (1H, d, *J* = 7.8, Ar*H*), 6.96 (1H, dd, *J* = 8.4, 2.4, Ar*H*), 6.99 (2H, d, *J* = 7.2, Ar*H*), 7.03 (1H, dd, *J* = 7.8, 1.8, Ar*H*), 7.19 (2H, t, *J* = 8.4, Ar*H*), 7.26-7.30 (2H, m, Ar*H*), 7.53 (1H, d, *J* = 7.2, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -67.42 (3F, s, C*F*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 34.2 (Ar*C*H$_2$), 55.5 (O*C*H$_3$), 55.6 (O*C*H$_3$), 62.9 (*C*HN), 87.1 (*C*HNO_2), 110.4 (*Ar*H), 113.6 (*Ar*H), 114.0 (*Ar*H), 116.4 (1C, q, *J* = 287.6, *C*F_3), 121.4 (*Ar*H), 122.7 (*Ar*), 127.0 (*Ar*), 128.7 (*Ar*H), 129.4 (*Ar*H), 129.5 (*Ar*H), 129.6 (*Ar*H), 130.7 (*Ar*H), 131.2 (*Ar*H), 132.9 (*Ar*), 133.1 (*Ar*H), 157.1 (*Ar*O), 158.1 (1C, q, *J* = 35.6, *C*=O), 160.4 (*Ar*O); *m/z* (EI) 488 (5, M); HRMS $C_{25}H_{23}F_3N_2O_5$ calcd. 488.1554, found 488.1540; anal. calcd. for $C_{25}H_{23}F_3N_2O_5$: C, 61.47; H, 4.75; N, 5.74; found C, 61.84; H, 4.75; N, 5.70%. **When prepared by general procedure O**. Imine 30a (0.200 mmol) afforded, after purification by column chromatography (4% Me_2CO/pet. ether and 40% CH_2Cl_2/pet. ether), **239ga** (63 mg, 0.129 mmol, 64% yield) as a yellow foam; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 90:10, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 7.3 min, t_r (minor) = 15.6 min, shows 98% *ee*; $[\alpha]_D^{25}$ = -64.3 ^{o} (c = 0.98, $CHCl_3$).

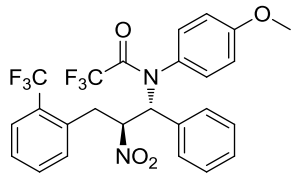
2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R,2*S**)-3-(4-methoxyphenyl)-2-nitro-1-phenylpropyl)acetamide 239ha**



When prepared by general procedure L. Nitroalkene **84h** (80 mg, 0.50 mmol) afforded after purification by column chromatography (10% EtOAc/pet. ether) *β*-nitrotrifluoroacetamide **239ha** (211 mg, 0.43 mmol, 86% yield) as a brown oil; IR υ_{max} 2935 (C-H), 2840 (C-H), 1697 (C=O), 1556 (N-O), 1510, 1301, 1250, 1207, 1179, 1155 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.43 (1H, dd, *J* = 14.4, 10.8, ArC*H*$_2$), 3.53 (1H, dd, *J* = 14.4, 3.0, ArC*H*$_2$), 3.77 (3H, s, OC*H*$_3$), 3.80 (3H, s,

OC*H*$_3$), 5.59 (1H, br. s, C*H*NO$_2$), 6.09 (1H, br. s, C*H*N), 6.40 (1H, br. s, Ar*H*), 6.72 (1H, dd, *J* = 9.0, 2.4, Ar*H*), 6.88 (2H, dm, *J* = 8.4, Ar*H*), 6.93 (1H, dd, *J* = 8.4, 3.0 Ar*H*), 7.08 (1H, d, *J* = 7.8, Ar*H*), 7.13 (2H, d, *J* = 7.2, Ar*H*), 7.16 (2H, dm, *J* = 9.0, Ar*H*), 7.24 (2H, t, *J* = 7.8, Ar*H*), 7.32 (1H, t, *J* = 7.8, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -67.6 (3F, s, C*F*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 37.6 (Ar*C*H$_2$), 55.3 (O*C*H$_3$), 55.6 (O*C*H$_3$), 65.2 (*C*HN), 90.0 (*C*HNO$_2$), 114.1 (*Ar*H), 114.6 (*Ar*H), 116.4 (1C, q, *J* = 288.7, *C*F$_3$), 126.5 (*Ar*), 128.0 (*Ar*), 128.9 (*Ar*H), 129.4 (*Ar*H), 129.8 (*Ar*H), 130.2 (*Ar*H), 132.2 (*Ar*H) 133.3 (*Ar*), 158.1 (1C, q, *J* = 35.5, *C*=O), 159.3 (*Ar*O), 160.6 (*Ar*O); *m/z* (EI) 488 (46, M); HRMS $C_{25}H_{23}F_3N_2O_5$ calcd. 488.1554, found 488.1550.

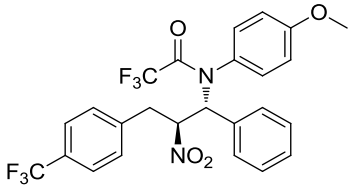
2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S*,2*R*)-2-nitro-1-phenyl-3-(2-(trifluoromethyl)phenyl)propyl)acetamide 239ia



When prepared by general procedure L. Nitroalkene **84i** (109 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me_2CO/pet. ether) *β*-nitrotrifluoroacetamide **239ia** (209 mg, 0.40 mmol, 79% yield) as an off-white solid; mp 108-112 ^{o}C; IR υ_{max} 2939 (C-H), 1698 (C=O), 1558 (N-O), 1511, 1315, 1209, 1180, 1110 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.65 (1H, dd, *J* = 14.4, 12.0, ArC*H*$_2$), 3.82 (3H, s, OC*H*$_3$), 3.85 (1H, dd, *J* = 15.0, 3.0, ArC*H*$_2$), 5.74 (1H, br. s, C*H*NO$_2$), 6.17 (1H, br. s, C*H*N), 6.33 (1H, br. s, Ar*H*), 6.65 (1H, d, *J* = 6.6, Ar*H*), 6.92 (1H, dd, *J* = 9.0, 3.0, Ar*H*), 7.10 (2H, d, *J* = 7.2, Ar*H*), 7.15 (1H, d, *J* = 7.8, Ar*H*), 7.24 (2H, t, *J* = 7.8, Ar*H*), 7.29-7.33 (2H, m, Ar*H*), 7.42 (1H, t, *J* = 7.8 Ar*H*), 7.51 (1H, t, *J* = 7.8, Ar*H*), 7.71 (1H, d, *J* = 7.8, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -59.5 (3F, s, ArC*F*$_3$), -67.7 (3F, s, C*F*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 35.1 (Ar*C*H$_2$), 55.6 (O*C*H$_3$), 65.8 (*C*HN), 88.5 (*C*HNO$_2$), 113.9 (*Ar*H), 114.5 (*Ar*H), 116.3 (1C, q, *J* = 288.7, F$_3$*C*C=O), 124.6 (1C, q, *J* = 273.9, F$_3$*C*Ar), 126.7 (1C, q, *J* = 5.7, *Ar*H), 128.3 (*Ar*H), 128.7 (1C, q, *J* = 30.0, *Ar*CF$_3$), 128.9 (*Ar*H), 129.8 (*Ar*H), 130.4 (*Ar*H), 131.8 (*Ar*H), 132.1 (*Ar*H), 132.7 (*Ar*) 132.8 (*Ar*H), 132.9 (*Ar*), 158.4 (1C, q, *J* = 36.2, *C*=O), 160.5 (*Ar*O); *m/z* (EI) 526 **(**27, M**)**, 262 (100, M-$C_9H_7N_2O_4$); HRMS $C_{25}H_{20}F_6N_2O_4$ calcd. 526.1322, found 526.1335; anal. calcd. for $C_{25}H_{20}F_6N_2O_4$: C,

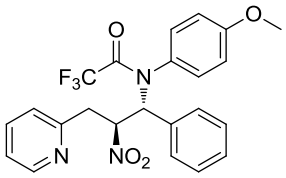
57.04; H, 3.83; N, 5.32; found C, 56.75; H, 3.71; N, 5.20. **When prepared by general procedure O**. Imine **30a** (0.200 mmol) afforded, after purification by column chromatography (4% Me_2CO/pet. ether and 40% CH_2Cl_2/pet. ether), **239ia** (77 mg, 0.146 mmol, 73% yield) as a yellow solid; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 90:10, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 5.2 min, t_r (minor) = 9.6 min, shows 95% *ee*; mp 109-111 ^oC; $[\alpha]_D^{25}$ = -69.0 ^{o} (c = 1.00, $CHCl_3$).

2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S,2*R**)-2-nitro-1-phenyl-3-(4-(trifluoromethyl)phenyl)propyl)acetamide 239ja**



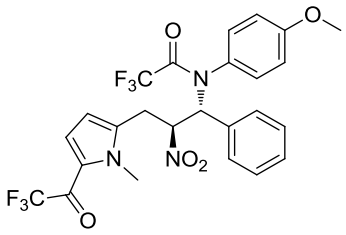
When prepared by general procedure L. Nitroalkene **84j** (109 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me_2CO/pet. ether) *β*-nitrotrifluoroacetamide **239ja** (213 mg, 0.41 mmol, 81% yield) as a yellow oil; IR υ_{max} 2939 (C-H), 1697 (C=O), 1557 (N-O), 1510, 1324, 1254, 1209, 1157, 1111 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.54 (1H, dd, *J* = 14.4, 11.4, ArC*H*$_2$), 3.60 (1H, dd, *J* = 14.4, 3.0, ArC*H*$_2$), 3.83 (3H, s, OC*H*$_3$), 5.69 (1H, br. s, C*H*NO_2), 5.95 (1H, br. s, C*H*N), 6.48 (1H, br. s, Ar*H*), 6.75 (1H, dd, *J* = 8.4, 1.8, Ar*H*), 6.92 (1H, dd, *J* = 8.4, 2.4, Ar*H*), 7.00 (1H, d, *J* = 7.8, Ar*H*), 7.13 (2H, d, *J* = 7.8, Ar*H*), 7.26 (2H, t, *J* = 7.8, Ar*H*), 7.34 (1H, t, *J* = 7.2, Ar*H*), 7.37 (2H, d, *J* = 7.8 Ar*H*), 7.61 (2H, d, *J* = 7.8, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -63.1 (3F, s, ArC*F*$_3$), -67.7 (3F, s, C*F*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.0 (Ar*C*H_2), 55.6 (O*C*H_3), 66.0 (*C*HN), 89.6 (*C*HNO_2), 114.2 (*Ar*H), 114.7 (*Ar*H), 116.3 (1C, q, *J* = 289.0, F_3*C*C=O), 124.1 (1C, q, *J* = 271.8, F_3*C*Ar), 126.2 (1C, q, *J* = 4.5, *Ar*H), 128.2 (br., *Ar*), 129.1 (*Ar*H), 129.2 (*Ar*H), 129.3 (*Ar*H), 130.0 (*Ar*H), 130.1 (*Ar*H), 130.4 (1C, q, *J* = 33.2, *Ar*CF_3), 131.9 (*Ar*H), 133.0 (*Ar*), 138.6 (*Ar*), 158.3 (1C, q, *J* = 35.9, *C*=O), 160.6 (*Ar*O); *m/z* (EI) 526 **(**7, M**)**, 261 (100, M-$C_9H_8N_2O_4$); HRMS $C_{25}H_{20}F_6N_2O_4$ calcd. 526.1322, found 526.1317; anal. calcd. for $C_{25}H_{20}F_6N_2O_4$: C, 57.04; H, 3.83; N, 5.32; found C, 56.99; H, 3.75; N, 5.25.

2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S*,2*R*)-2-nitro-1-phenyl-3-(pyridin-2-yl)propyl)acetamide 239ka



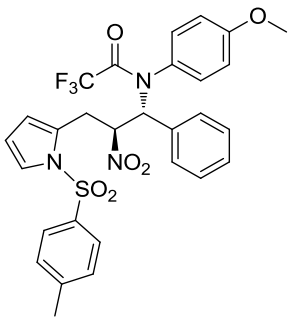
When prepared by general procedure L. Nitroalkene **84k** (75 mg, 0.50 mmol) afforded after purification by column chromatography (20% EtOAc/pet. ether) *β*-nitrotrifluoroacetamide **239ka** (149 mg, 0.32 mmol, 65% yield) as a yellow oil; IR υ_{max} 2935 (C-H), 1696 (C=O), 1555 (N-O), 1255, 1206, 1180, 1152 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.66 (1H, dd, *J* = 15.0, 10.5, PhCH_2), 3.72 (1H, dd, *J* = 15.0, 3.5, PhCH_2), 3.82 (3H, s, OCH_3), 5.94 (1H, apt. td, *J* = 11.0, 3.5, C*H*NO_2), 6.13 (1H, d, *J* = 7.0, Ar*H*), 6.50 (1H, d, *J* = 11.5, C*H*N), 6.60 (1H, dd, *J* = 8.5, 3.0, Ar*H*), 7.01 (1H, dd, *J* = 9.0, 3.0, Ar*H*), 7.04 (2H, d, *J* = 7.5, Ar*H*), 7.15 (1H, d, *J* = 7.5, Ar*H*), 7.20-7.23 (3H, m, Ar*H*), 7.30 (1H, m, Ar*H*), 7.52 (1H, dd, *J* = 8.5, 2.5, Ar*H*), 7.63 (1H, td, *J* = 7.5, 2.0, Ar*H*), 8.65 (1H, m, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -67.3 (s, CF_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 40.3 (Ar*C*H_2), 55.6 (O*C*H_3), 62.5 (*C*HN), 87.8 (*C*HNO_2), 114.0 (*Ar*H), 114.1 (*Ar*H), 116.4 (1C, q, *J* = 288.4, *C*F_3), 122.8 (*Ar*H), 123.8 (*Ar*H), 126.6 (*Ar*), 128.7 (*Ar*H), 129.5 (*Ar*H), 129.7 (*Ar*H), 131.0 (*Ar*H), 132.6 (*Ar*), 133.0 (*Ar*H), 137.1 (*Ar*H), 150.2 (*Ar*H), 155.1 (*Ar*), 158.3 (1C, q, *J* = 36.2, *C*=O), 160.5 (*Ar*O); *m/z* (ESI^+) 560 (86, M+H), 413 (48, M-NO_2); HRMS $C_{23}H_{20}F_3N_3O_4H^+$ calcd. 460.1484, found 460.1494. **When prepared by general procedure O**. Imine 30a (0.20 mmol) afforded, after purification by column chromatography (4% Me_2CO/pet. ether and 40% CH_2Cl_2/pet. ether), **239ka** (62 mg, 0.135 mmol, 68% yield) as a pink solid; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 80:20, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 6.9 min, t_r (minor) = 12.9 min, shows 98% *ee*; mp 100-102 ^{o}C; $[\alpha]_D^{25}$ = -25.6 ^{o} (c = 1.01, $CHCl_3$).

2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S,2*R**)-3-(1-methyl-5-(2,2,2-trifluoro acetyl)-1*H*-pyrrol-2-yl)-2-nitro-1-phenylpropyl)acetamide 240ma**



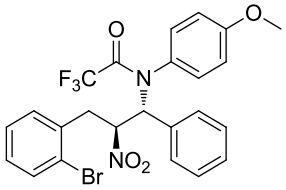
When prepared by general procedure L. Nitroalkene **84m** (76 mg, 0.50 mmol) afforded after purification by column chromatography (50% CH_2Cl_2/pet. ether) *β*-nitrotrifluoroacetamide **240ma** (175 mg, 0.32 mmol, 63% yield) as a yellow foam; IR υ_{max} 2963 (C-H), 1686 (C=O), 1672 (C=O), 1560 (N-O), 1511, 1210, 1181, 1147 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.48 (1H, d, *J* = 16.0, ArC*H*$_2$), 3.68 (1H, dd, *J* = 16.0, 11.0, ArC*H*$_2$), 3.83 (3H, s, OC*H*$_3$), 3.98 (3H, s, NC*H*$_3$), 5.8 (2H, br. s, C*H*N, C*H*NO_2), 6.25 (1H, d, *J* = 4.4, Ar*H*), 6.54 (1H, br. s, Ar*H*), 6.78 (1H, dd, *J* = 8.7, 2.3, Ar*H*), 6.84 (1H, d, *J* = 8.5, Ar*H*), 6.88 (1H, dd, *J* = 8.7, 2.6, Ar*H*), 7.15 (2H, d, *J* = 7.6, Ar*H*), 7.20 (1H, dd, *J* = 4.0, 1.9, Ar*H*), 7.29 (2H, t, *J* = 7.7, Ar*H*), 7.37 (1H, t, *J* = 7.4, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$), δ -71.6 (3F, s, C*F*$_3$), -67.7 (3F, s, C*F*$_3$); *m/z* (ESI^+), 558 (18, M+H), 511 (32, M-NO_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 29.2 (Ar*C*H_2), 33.7 (*C*H_3), 55.7 (O*C*H_3), 66.8 (*C*HN), 87.0 (*C*HNO_2), 110.9 (*Ar*H), 114.2 (*Ar*H), 114.9 (*Ar*H), 116.2 (1C, q, *J* = 288.7, *C*F_3), 117.1 (1C, q, *J* = 290.8, *C*F_3), 124.0 (1C, q, *J* = 3.9, *Ar*H), 125.9 (*Ar*), 128.3 (*Ar*), 129.2 (*Ar*H), 129.4 (*Ar*H), 130.1 (*Ar*H), 130.2 (*Ar*H), 131.5 (*Ar*H), 132.6 (*Ar*), 158.5 (1C, q, *J* = 36.2, *C*=O), 160.7 (*Ar*O), 170.1 (1C, q, *J* = 34.7, *C*=O); *m/z* (ESI^+) 558 (8, M+H), 511 (32, M-NO_2); HRMS $C_{25}H_{21}F_6N_3O_5H^+$ calcd. 558.1464, found 558.1451.

2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S,2*R**)-2-nitro-1-phenyl-3-(1-tosyl-1 *H*-pyrrol-2-yl)propyl)acetamide 239na**



When prepared by general procedure L. Nitroalkene **84n** (113 mg, 0.39 mmol) afforded after purification by column chromatography (50% CH_2Cl_2/pet. ether) *β*-nitrotrifluoroacetamide **239na** (173 mg, 0.29 mmol, 74% yield) as a yellow foam; IR υ_{max} 2968 (C-H), 1698 (C=O), 1558 (N-O), 1512, 1366, 1208, 1180, 1153 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.41 (3H, s, ArC*H*$_3$), 3.60 (1H, dd, *J* = 15.8, 11.2, ArC*H*$_2$), 3.70 (1H. dd. *J* = 15.7, 3.1, ArC*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 5.62 (1H, apt. td, *J* = 11.0, 2.5, C*H*NO_2), 6.07-6.13 (2H, m, Ar*H*), 6.22 (1H, t, *J* = 3.4, Ar*H*), 6.34 (1H, d, *J* = 9.9, C*H*N), 6.53 (1H, dd, *J* = 8.8, 2.8, Ar*H*), 6.93-6.98 (3H, m, Ar*H*), 7.17 (2H, t, *J* = 7.8, Ar*H*), 7.24-7.28 (1H, m, Ar*H*), 7.31 (2H, d, *J* = 8.2, Ar*H*), 7.34 (1H, dd, *J* = 3.3, 1.6, Ar*H*), 7.60 (1H, d, *J* = 7.7, Ar*H*), 7.63 (2H, d, *J* = 8.4, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$), δ-67.38 (3F, s, C*F*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.8 (Ar*C*H_3), 30.8 (Ar*C*H_2), 55.6 (O*C*H_3), 63.9 (*C*HN), 88.2 (*C*HNO_2), 112.6 (*Ar*H), 113.8 (*Ar*H), 114.2 (*Ar*H), 116.4 (*Ar*H), 116.4 (1C, q, *J* = 288.9, *C*F_3), 124.1 (*Ar*H), 126.5 (*Ar*H), 127.2 (*Ar*), 127.3 (*Ar*), 128.7 (*Ar*H), 129.6 (*Ar*H), 129.7 (*Ar*H), 130.5 (*Ar*H), 131.0 (*Ar*H), 132.4 (*Ar*), 132.7 (*Ar*H), 135.8 (*Ar*), 145.7 (*Ar*), 158.4 (1C, q, *J* = 35.6, *C*=O), 160.3 (*Ar*O); *m/z* (ESI^+) 624 (56, M+Na), 555 (100, M-NO_2); HRMS $C_{29}H_{26}F_3N_3O_6SNa^+$ calcd. 624.1384, found 624.1392.

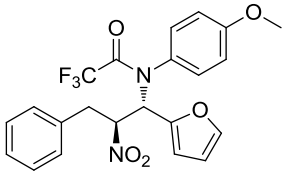
_N_-((1_R_,2_S_)-3-(2-Bromophenyl)-2-nitro-1-phenylpropyl)-2,2,2-trifluoro-_N_-(4-methoxyphenyl)acetamide 239oa



Prepared by general procedure O. Nitroalkene **84o** (6.00 mmol) afforded, after purification by column chromatography (10% Me_2CO/pet. ether and 40% CH_2Cl_2/pet. ether), **239oa** (1.27 g, 2.36 mmol, 79% yield, 98% *ee*) as a white solid; ; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 95:5, flow rate = 1 mL/min, *λ* = 254 nm): retention time t_r (major) = 8.0 min, t_r (minor) = 16.1 min, shows 98% *ee*; which after recrystallisation (*iso*-propanol) gave enantiopure **239oa** (990 mg, 1.84 mmol, 61% yield) as a white solid; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 95:5, flow rate = 1 mL/min, *λ* = 254 nm): retention time t_r (major) = 8.0 min, t_r (minor) = 16.1 min, shows >99% *ee*; mp 128-130 ^oC; $[\alpha]_D^{25}$ = -114.7 (c = 0.97, $CHCl_3$, after recrystallisation (*iso*-propanol) to >99% *ee*); ^1H NMR (600 MHz, $CDCl_3$) δ 3.59 (1H,

dd, J = 14.3, 11.5, ArCH_2), 3.78 (1H, dd, J = 14.3, 3.8, ArCH_2), 3.81 (3H, s, OCH_3), 5.74 (1H, br. t, J = 10.0, CHNO_2), 6.25 (1H, br. s, ArH), 6.31 (1H, br. s, CHN), 6.62 (1H, dd, J = 8.7, 2.6, ArH), 6.91 (1H, dd, J = 8.8, 2.9, ArH), 7.06 (2H, d, J = 7.5, ArH), 7.15-7.20 (2H, m, ArH), 7.22 (2H, t, J = 7.7, ArH), 7.24-7.28 (1H, m, ArH), 7.28-7.32 (1H, m, ArH), 7.41 (1H, br. d, J = 7.9, ArH), 7.61 (1H, dd, J = 8.1, 1.1, ArH). ^{1}H NMR data are consistent with literature data.[127]

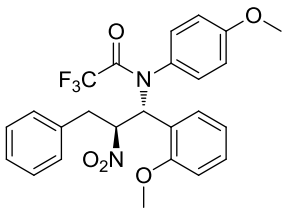
2,2,2-Trifluoro-*N*-((1*R*,2*R*)-1-(furan-2-yl)-2-nitro-3-phenylpropyl)-*N*-(4-methoxy phenyl)acetamide 239ab



When prepared by general procedure M. Nitroalkene **84a** (75 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me_2CO/pet. ether) β-nitrotrifluoroacetamide **239ab** (186 mg, 0.42 mmol, 83% yield) as a yellow solid; mp 120-123 ^{o}C; IR υ_{max} 2937 (C-H), 1698 (C=O), 1557 (N-O), 1509, 1253, 1207, 1180, 1152 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.41 (1H, dd, J = 14.4, 10.8, PhCH-$_2$), 3.49 (1H, dd, J = 15.0, 3.6, PhCH_2), 3.83 (3H, s, OCH_3), 5.35 (1H, apt. td, J = 11.4, 3.6, CHNO_2), 6.27, (2H, dd, J = 0.6, ArH), 6.33 (1H, d, J = 10.8, CHN), 6.47 (1H, d, J = 8.4, ArH), 6.75 (1H, dd, J = 9.0, 2.4, ArH), 6.96 (1H, dd, J = 8.4, 6.0, ArH), 7.20 (3H, d, J = 7.2, ArH), 7.29-7.37 (4H, m, ArH); ^{19}F NMR (300 MHz, $CDCl_3$) δ -67.7 (3F, s, CF_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 37.8 (PhCH$_2$), 55.6 (OCH$_3$), 58.0 (CHN), 88.6 (CHNO$_2$), 111.0 (ArH), 111.9 (ArH), 114.2 (ArH), 114.7 (ArH), 116.2 (1C, q, J = 288.7, CF$_3$), 127.9 (Ar), 128.1 (ArH), 128.7 (ArH), 129.2 (ArH), 130.0 (ArH), 131.1 (ArH), 134.3 (Ar), 143.4 (ArH), 146.2 (Ar), 158.0 (1C, q, J = 36.2, C=O), 160.6 (ArO); *m/z* (CI) 449 **(**24, M+H**)**, 402 (97, M-NO$_2$); HRMS $C_{22}H_{19}F_3N_2O_5H^+$ calcd. 449.1324, found 449.1313; anal. calcd. for $C_{22}H_{19}F_3N_2O_5$: C, 58.93; H, 4.27; N, 6.25; found C, 59.07; H, 4.20; N, 6.21. **When prepared by general procedure O**. Imine **30b** (0.200 mmol) afforded, after purification by column chromatography (4% Me_2CO/pet. ether and 40% CH_2Cl_2/pet. ether), **239ab** (69 mg, 0.154 mmol, 77% yield) as an orange foamy solid; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 97.5:2.5, flow rate = 1 mL/min, λ = 254 nm): retention time

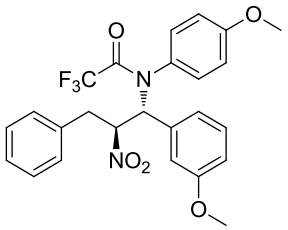
t_r (major) = 11.6 min, t_r (minor) = 17.5 min, shows 97% *ee*; mp 53-54 ^oC; $[\alpha]_D^{25}$ = -104.3 ^{o} (c = 1.04, $CHCl_3$).

2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S*,2*R*)-1-(2-methoxyphenyl)-2-nitro-3-phenylpropyl)acetamide 239ac



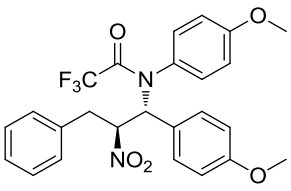
When prepared by general procedure M. Nitroalkene **84a** (75 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me_2CO/pet. ether) *β*-nitrotrifluoroacetamide **239ac** (212 mg, 0.43 mmol, 87% yield) as a yellow solid; mp 136-140 ^oC; IR υ_{max} 2940 (C-H), 1698 (C=O), 1555 (N-O), 1510, 1495, 1298, 1252, 1206, 1180, 1152 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.50-3.57 (2H, m, PhC*H*$_2$), 3.77 (3H, s, OC*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 5.48 (1H, m, C*H*NO_2), 6.20 (1H, d, *J* = 7.8, Ar*H*), 6.59 (1H, dd, *J* = 8.8, 2.8, Ar*H*), 6.70 (1H, t, *J* = 7.5 Ar*H*), 6.79 (1H, br. d, *J* = 11.0, C*H*N), 6.83 (1H, br. d, *J* = 6.2, Ar*H*), 6.86 (1H, d, *J* = 8.2, Ar*H*), 6.92 (1H, dd, *J* = 8.7, 2.9, Ar*H*), 7.08 (1H, dd, *J* = 8.6, 2.1, Ar*H*), 7.23-7.28 (3H, m, Ar*H*), 7.30 (1H, m, Ar*H*), 7.36 (2H, t, *J* = 7.6, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -67.5 (3F, s, C*F*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.4 (Ph*C*H_2), 55.6 (O*C*H_3), 55.7 (O*C*H_3), 57.3 (*C*HN), 89.2 (*C*HNO_2), 110.9 (*Ar*H), 113.7 (*Ar*H), 114.1 (*Ar*H), 116.5 (1C, q, *J* = 288.9, *C*F_3), 120.4 (*Ar*H), 121.3 (*Ar*), 127.7 (*Ar*), 127.9 (*Ar*H), 128.7 (*Ar*H), 129.2 (*Ar*H), 130.1 (*Ar*H), 130.8 (*Ar*H), 132.2 (*Ar*H), 135.0 (*Ar*), 157.9 (1C, q, *J* = 35.5, *C*=O), 157.9 (*Ar*O), 160.3 (*Ar*O); *m/z* (EI) 488 (8, M), 224 (100, M-$C_9H_7F_3N_2O_4$); HRMS $C_{25}H_{23}F_3N_2O_5$ calcd. 488.1554, found 488.1543; anal. calcd. for $C_{25}H_{23}F_3N_2O_5$: C, 61.47; H, 4.75; N, 5.74; found C, 61.28; H, 4.57; N, 5.70. **When prepared by general procedure O**. Imine **30c** (0.200 mmol) afforded, after purification by column chromatography (4% Me_2CO/pet. ether and 40% CH_2Cl_2/pet. ether), **239ac** (81 mg, 0.166 mmol, 83% yield) as a yellow foamy solid; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 97.5:2.5, flow rate = 1 mL/min, *λ* = 254 nm): retention time t_r (minor) = 12.2 min, t_r (major) = 15.3 min, shows 99% *ee*; mp 49-51 ^oC; $[\alpha]_D^{25}$ = -69.1 ^{o} (c = 1.03, $CHCl_3$).

2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S,2*R**)-1-(3-methoxyphenyl)-2-nitro-3-phenylpropyl)acetamide 239ad**



When prepared by general procedure M. Nitroalkene **84a** (75 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me_2CO/pet. ether) *β*-nitrotrifluoroacetamide **239ad** (210 mg, 0.43 mmol, 86% yield) as a yellow solid; mp 130-134 ^oC; IR υ_{max} 2938 (C-H), 1697 (C=O), 1557 (N-O), 1510, 1254, 1207, 1180, 1154 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.48 (1H, dd, *J* = 14.4, 11.4, PhC*H*$_2$), 3.59 (1H, dd, *J* = 15.0, 3.0, PhC*H*$_2$), 3.68 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 5.62 (1H, br. s, C*H*NO_2), 6.07 (1H, br. s, C*H*N), 6.48 (1H, br. s, Ar*H*), 6.70 (2H, br. s, Ar*H*), 6.74 (1H, dd, *J* = 9.0, 2.4, Ar*H*), 6.87 (1H, dd, *J* = 7.8, 1.8 Ar*H*), 6.94 (1H, dd, *J* = 9.0, 3.0, Ar*H*), 7.09 (1H, br. d, *J* = 7.8 Ar*H*), 7.15 (1H, t, *J* = 7.8, Ar*H*), 7.26 (2H, d, *J* = 7.2, Ar*H*), 7.31 (1H, t, *J* = 7.2, Ar*H*), 7.36 (2H, t, *J* = 7.2, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -67.5 (3F, s, C*F*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.4 (Ph*C*H_2), 55.3 (O*C*H_3), 55.6 (O*C*H_3), 65.2 (*C*HN), 89.8 (*C*HNO_2), 114.1 (*Ar*H), 114.6 (*Ar*H), 114.7 (*Ar*H), 115.6 (*Ar*H), 116.4 (1C, q, *J* = 289.0, *C*F_3), 121.6 (*Ar*H), 128.1 (*Ar*H), 128.8 (*Ar*H), 129.2 (*Ar*H), 129.9 (*Ar*H), 130.2 (*Ar*H), 132.2 (*Ar*H), 134.5 (*Ar*), 134.6 (*Ar*), 158.2 (1C, q, *J* = 35.9, *C*=O), 159.8 (*Ar*O), 160.6 (*Ar*O); *m/z* (EI) 488 (5, M); HRMS $C_{25}H_{23}F_3N_2O_5$ calcd. 488.1554, found 488.1558; anal. calcd. for $C_{25}H_{23}F_3N_2O_5$: C, 61.47; H, 4.75; N, 5.74; found C, 61.40; H, 4.67; N, 5.72.

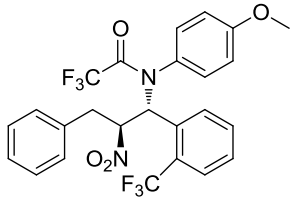
2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S*,2*R*)-1-(4-methoxyphenyl)-2-nitro-3-phenylpropyl)acetamide 239ae



When prepared by general procedure M. Nitroalkene **84a** (75 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me_2CO/pet. ether)

β-nitrotrifluoroacetamide **239ae** (195 mg, 0.40 mmol, 80% yield) as a brown oil; IR υ_{max} 2939 (C-H), 1695 (C=O), 1555 (N-O), 1512, 1252, 1209, 1183, 1152 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.48 (1H, dd, *J* = 14.6, 10.9, ArCH_2), 3.57 (1H, dd, *J* = 14.6, 3.2, ArCH_2), 3.80 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.59 (1H, br. t, *J* = 9.5, C*H*NO_2), 6.01 (1H, br. s, C*H*N), 6.47 (1H, br. d, *J* = 7.2, Ar*H*), 6.70-6.80 (3H, m, Ar*H*), 6.95 (1H, dd, *J* = 8.7, 2.8, Ar*H*), 7.00-7.10 (3H, m, Ar*H*), 7.20-7.30 (2H, m, Ar*H*), 7.30-7.40 (3H, m, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ-67.6 (3F, s, CF_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.3 (Ph*C*H_2), 55.4 (O*C*H_3), 55.7 (O*C*H_3), 64.9 (*C*HN), 90.1 (*C*HNO_2), 114.1 (*Ar*H), 114.2 (*Ar*H), 114.6 (*Ar*H), 116.3 (1C, q, *J* = 291.4, *C*F_3), 125.0 (*Ar*), 128.0 (*Ar*H), 128.7 (*Ar*H), 129.2 (*Ar*H), 130.2 (*Ar*H), 130.7 (*Ar*H) 132.3 (*Ar*H), 134.7 (*Ar*), 158.1 (1C, q, *J* = 34.7, *C*=O), 160.5 (2C, *Ar*O); *m/z* (EI) 488 (4, M), 441 (3, M-NO_2H); HRMS $C_{25}H_{23}F_3N_2O_5$ calcd. 488.1554, found 488.1557; anal. calcd. for $C_{25}H_{23}F_3N_2O_5$: C, 61.47; H, 4.75; N, 5.74; found C, 61.40; H, 4.68; N, 5.70. **When prepared by general procedure O**. Imine **30e** (0.20 mmol) afforded, after purification by column chromatography (10% EtOAc/pet. ether and 50% CH_2Cl_2/pet. ether), **239ae** (73 mg, 0.150 mmol, 75% yield) as a yellow solid; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 90:10, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 8.6 min, t_r (minor) = 15.4 min, shows 97% *ee*; mp 59-61 ^{o}C; $[\alpha]_D^{25}$ = -58.7 ^{o} (c = 0.87, $CHCl_3$).

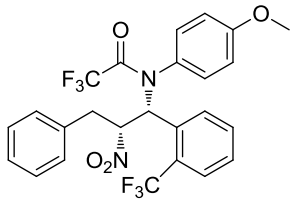
2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S*,2*R*)-2-nitro-3-phenyl-1-(2-(trifluoro methyl)phenyl)propyl)acetamide 239af



When prepared by general procedure M. Nitroalkene **84a** (75 mg, 0.50 mmol) afforded after purification by column chromatography (7.5% EtOAc/pet. ether) *β*-nitrotrifluoroacetamide **239af** (201 mg, 0.38 mmol, 76% yield) as a yellow sticky solid; mp 126-128 ^{o}C; IR υ_{max} 2939 (C-H), 1704 (C=O), 1557 (N-O), 1511, 1312, 1209, 1181, 1154, 1121 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.53 (1H, dd, *J* = 15.0, 3.0, PhCH_2), 3.64 (1H, dd, *J* = 15.0, 11.4, PhCH_2), 3.80 (3H, s, O CH_3), 5.40 (1H, apt. td, *J* = 11.4, 3.0, C*H*NO_2), 6.04 (1H, dd, *J* = 9.0, 1.8, Ar*H*), 6.51 (1H, dd, *J* = 9.0, 3.0, Ar*H*), 6.68 (1H, d, *J* = 5.4, Ar*H*), 6.98 (1H, dd, *J* = 8.4, 3.0, Ar*H*), 7.06 (1H,

d, *J* = 10.9, C*H*N), 7.14-7.19 (2H, m, Ar*H*), 7.23-7.26 (2H, m, Ar*H*), 7.32 (1H, t, *J* = 7.2, Ar*H*), 7.35-7.41 (3H, m, Ar*H*), 7.74 (1H, d, *J* = 7.8, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -67.7 (3F, s, CF_3), -60.2 (3F, s, ArCF_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.3 (Ph*C*H_2), 55.6 (O*C*H_3), 57.1 (*C*HN), 89.9 (*C*HNO_2), 114.0 (*Ar*H), 114.4 (*Ar*H), 116.3 (1C, q, *J* = 288.7, F_3*C*C=O), 127.0 (1C, q, *J* = 274.4, F_3*C*Ar), 126.4 (*Ar*), 127.0 (1C, q, *J* = 5.7, *Ar*H), 128.1 (*Ar*H), 128.7 (*Ar*H), 129.3 (*Ar*H), 129.8 (*Ar*H), 130.2 (*Ar*), 130.3 (1C, q, *J* = 30.7, *Ar*CF_3), 130.4 (*Ar*H), 131.3 (*Ar*H), 133.0 (*Ar*H), 134.7 (*Ar*), 157.9 (1C, q, *J* = 35.9, *C*=O), 160.6 (*Ar*O); *m/z* (EI) 526 (7, M), 261 (100, M-$C_9H_8N_2O_4$); HRMS $C_{25}H_{20}F_6N_2O_4$ calcd. 526.1322, found 526.1327; anal. calcd. for $C_{25}H_{20}F_6N_2O_4$: C, 57.04; H, 3.83; N, 5.32; found C, 56.79; H, 3.69; N, 5.30. **When prepared by general procedure O**. Imine **30f** (0.200 mmol) afforded, after purification by column chromatography (10-20% EtOAc/pet. ether and 40-50% CH_2Cl_2/pet. ether), major diastereomer **239af** (70 mg, 0.133 mmol, 67% yield) as a white solid; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 97.5:2.5, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 9.0 min, t_r (minor) = 11.0 min, shows 80% *ee*; mp 128-130 ^{o}C; $[\alpha]_D^{25}$ = -28.2 ^{o} (c = 1.06, $CHCl_3$).

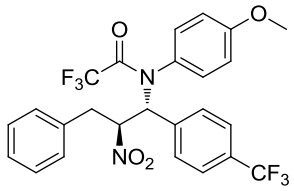
2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S*,2*S*)-2-nitro-3-phenyl-1-(2-(trifluoro methyl)phenyl)propyl)acetamide 239af *syn*



When prepared by general procedure O. Imine **30f** (0.200 mmol) afforded, after purification by column chromatography (10-20% EtOAc/pet. ether and 40-50% CH_2Cl_2/pet. ether), minor diastereomer **239af *syn*** (16 mg, 0.030 mmol, 15% yield) as a white solid; HPLC analysis (Chiralcel OD-H 15 cm, hexane/*iso*-propanol 95:5, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 7.8 min, t_r (minor) = 9.0 min, shows 8% *ee*; mp 150-152 ^{o}C; IR υ_{max} 1706 (C=O), 1561 (N-O), 1511 (N-O), 1313 (N-O), 1207, 1156, 1120 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.60 (1H, dd, *J* = 15.1, 2.4, PhCH_2), 3.26 (1H, dd, *J* = 15.0, 11.4, PhCH_2), 3.81 (3H, s, OCH_3), 5.63 (1H, br. s, C*H*NO_2), 6.27 (1H, br. d, *J* = 6.6, C*H*N), 6.61 (1H, dd, *J* = 8.8, 2.8, Ar*H*), 6.74 (1H, br. s, Ar*H*), 6.80 (1H, br. s, Ar*H*), 6.90 (1H, dd, *J* = 8.7, 2.8, Ar*H*), 6.97-7.02 (2H, m, Ar*H*), 7.19-7.29 (3H, m, Ar*H*), 7.38 (1H, t, *J* = 7.6, Ar*H*), 7.42 (1H, d, *J*

= 5.5, Ar*H*), 7.51 (1H, t, *J* = 7.6, Ar*H*), 7.81 (1H, d, *J* = 7.7, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -67.5; ^{13}C NMR (151 MHz, $CDCl_3$) δ 37.0 (Ph*C*H_2), 55.6 (O*C*H_3), 59.8 (*C*HN), 90.2 (*C*HNO_2), 114.0 (*Ar*H), 114.4 (*Ar*H), 116.1 (1C, q, *J* = 289.1, *C*F_3), 123.7 (1C, q, *J* = 274.2, Ar*C*F_3), 127.1 (1C, q, *J* = 6.0, *Ar*H), 127.4 (*Ar*), 127.8 (*Ar*H), 128.6 (*Ar*H), 129.1 (*Ar*H), 129.9 (*Ar*H), 130.6 (1C, q, *J* = 30.4, *Ar*CF_3), 130.9 (*Ar*H), 131.4 (*Ar*), 131.5 (*Ar*H), 132.0 (*Ar*H), 132.5 (*Ar*H), 134.7 (*Ar*), 157.2 (1C, q, *J* = 36.4, *C*=O), 160.5 (*Ar*O); *m/z* (CI) 527 (100, M+H); HRMS $C_{25}H_{20}F_6N_2O_4$ calcd. 527.1406, found 527.1407.

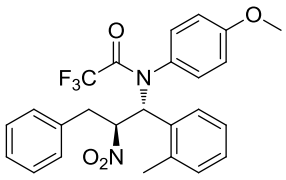
2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S*,2*R*)-2-nitro-3-phenyl-1-(4-(trifluoro methyl)phenyl)propyl)acetamide 239ag



When prepared by general procedure M. Nitroalkene **84a** (75 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me_2CO/pet. ether and then neat Toluene) *β*-nitrotrifluoroacetamide **239ag** (204 mg, 0.39 mmol, 78% yield) as a yellow solid; mp 122-126 ^{o}C; IR υ_{max} 2941 (C-H), 1700 (C=O), 1557 (N-O), 1510, 1325, 1211, 1165, 1119 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.50 (1H, dd, *J* = 14.4, 11.4, PhC*H*$_2$), 3.62 (1H, dd, *J* = 14.4, 2.4, PhC*H*$_2$), 3.82 (3H, s, OC*H*$_3$), 5.70 (1H, br. s, C*H*NO_2), 6.11 (1H, br. s, C*H*N), 6.49 (1H, br. s, Ar*H*), 6.78 (1H, d, *J* = 6.6, Ar*H*), 6.97 (1H, dd, *J* = 8.4, 2.4, Ar*H*), 7.08 (1H, br. d, *J* = 7.2, Ar*H*), 7.26 (2H, d, *J* = 7.2, Ar*H*), 7.29-7.34 (3H, m, Ar*H*), 7.37 (2H, t, *J* = 7.2, Ar*H*), 7.55 (2H, d, *J* = 7.8 Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -63.3 (3F, s, ArC*F*$_3$), -67.7 (3F, s, C*F*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.3 (Ph*C*H_2), 55.6 (O*C*H_3), 65.0 (*C*HN), 89.7 (*C*HNO_2), 114.4 (*Ar*H), 114.8 (*Ar*H), 116.3 (1C, q, *J* = 289.0, F_3C), 123.8 (1C, q, *J* = 272.9, F_3CAr), 125.9 (1C, q, *J* = 3.6, *Ar*H), 127.9 (*Ar*), 128.2 (*Ar*H), 128.7 (*Ar*H), 129.3 (*Ar*H), 129.9 (*Ar*H), 130.2 (*Ar*H), 131.9 (*Ar*H), 131.9 (1C, q, *J* = 32.6, *Ar*CF_3), 134.3 (*Ar*), 137.2 (*Ar*), 158.4 (1C, q, *J* = 35.9, *C*=O), 160.8 (*Ar*O); *m/z* (EI) 526 (100, M**)**, 261 (100, M-$C_9H_8N_2O_4$); HRMS $C_{25}H_{20}F_6N_2O_4$ calcd. 526.1322, found 526.1319; anal. calcd. for $C_{25}H_{20}F_6N_2O_4$: C, 57.04; H, 3.83; N, 5.32; found C, 57.02; H, 3.76; N, 5.32. **When prepared by general procedure O**. Imine **30g** (0.200 mmol) afforded, after purification by column chromatography (10% EtOAc/pet. ether and 40%

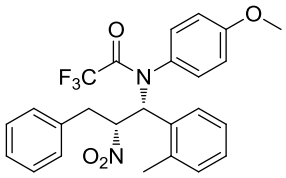
CH_2Cl_2/pet. ether), **239ag** (78 mg, 0.148 mmol, 74% yield) as a yellow foamy solid; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 97.5:2.5, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 8.2 min, t_r (minor) = 10.9 min, shows 94% *ee*; mp 48-50 ^oC; $[\alpha]_D^{25}$ = -55.7 ^{o} (c = 0.91, $CHCl_3$).

2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S*,2*R*)-2-nitro-3-phenyl-1-(*o*-tolyl) propyl)acetamide 239ah



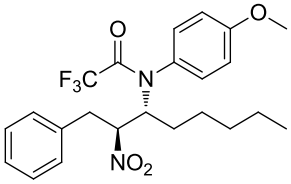
When prepared by general procedure M. Nitroalkene **84a** (75 mg, 0.50 mmol) afforded after purification by column chromatography (10% EtOAc/pet. ether and then neat Toluene) *β*-nitrotrifluoroacetamide **239ah** (169 mg, 0.36 mmol, 72% yield) as an off-white solid; mp 143-145 ^oC; IR υ_{max} 2938 (C-H), 1696 (C=O), 1556 (N-O), 1510, 1255, 1207, 1180, 1154 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.36 (3H, s, ArC*H*$_3$), 3.56 (2H, m, PhC*H*$_2$), 3.81 (3H, s, OC*H*$_3$), 5.47 (1H, br. s, C*H*NO_2), 6.13 (1H, br. s, Ar*H*), 6.59 (1H, dd, *J* = 8.4, 2.4, Ar*H*), 6.66 (2H, br. s, C*H*N, Ar*H*), 6.89 (1H, t, *J* = 7.2, Ar*H*), 6.93 (1H, dd, *J* = 8.4, 3.0, Ar*H*), 7.07 (1H, d, *J* = 7.8, Ar*H*), 7.15-7.20 (2H, m, Ar*H*), 7.25 (2H, d, *J* = 7.8, Ar*H*), 7.32 (1H, t, *J* = 7.2, Ar*H*), 7.37 (2H, t, *J* = 7.2, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -67.2 (3F, s, C*F*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 19.8 (Ar*C*H_3), 38.4 (Ph*C*H_2), 55.6 (O*C*H_3), 59.2 (*C*HN), 89.7 (*C*HNO_2), 113.9 (*Ar*H), 114.6 (*Ar*H), 116.5 (1C, q, *J* = 290.5, *C*F_3), 125.9 (*Ar*H), 127.0 (*Ar*), 128.0 (*Ar*H), 128.2 (*Ar*H), 128.7 (*Ar*H), 129.2 (*Ar*H), 129.5 (*Ar*H), 130.0 (*Ar*H), 131.0 (*Ar*), 131.2 (*Ar*H), 132.8 (*Ar*H), 134.8 (*Ar*), 138.1 (*Ar*), 158.2 (1C, q, *J* = 34.1, *C*=O), 160.5 (*Ar*O); *m/z* (EI) 472 (14, M**)**, 426 (8, M-NO_2); HRMS $C_{25}H_{23}F_3N_2O_4$ calcd. 472.1604, found 472.1607; anal. calcd. for $C_{25}H_{23}F_3N_2O_4$: C, 63.55; H, 4.91; N, 5.93; found C, 63.26; H, 4.82; N, 5.86. **When prepared by general procedure O**. Imine **30h** (0.200 mmol) afforded, after purification by column chromatography (10% EtOAc/pet. ether and 50% CH_2Cl_2/pet. ether), major diastereomer **239ah** (71 mg, 0.150 mmol, 75% yield) as a yellow foamy solid; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 99:1, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 10.5 min, t_r (minor) = 14.6 min, shows 90% *ee*; mp 60-61 ^oC; $[\alpha]_D^{25}$ = -67.2 ^{o} (c = 0.69, $CHCl_3$).

2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S*,2*S*)-2-nitro-3-phenyl-1-(*o*-tolyl) propyl)acetamide 239ah *syn*



When prepared by general procedure O. Imine **30h** (0.200 mmol) afforded, after purification by column chromatography (10% EtOAc/pet. ether and 50% CH_2Cl_2/pet. ether), minor diastereomer **239ah *syn*** (11 mg, 0.023 mmol, 12% yield) as an off-white solid; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 99:1, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 12.7 min, t_r (minor) = 16.0 min, shows 34% *ee*; mp 123-124 ^oC; IR υ_{max} 2925 (C-H), 1700 (C=O), 1557 (N-O), 1511, 1254, 1206, 1156 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.44 (3H, s, ArC*H*$_3$), 2.84 (1H, dd, *J* = 14.9, 2.3, PhC*H*$_2$), 3.13 (1H, dd, *J* = 14.8, 11.2, PhC*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 5.53 (1H, br. t, *J* = 10.2, C*H*NO_2), 6.13 (1H, br. d, *J* = 6.2, C*H*N), 6.55 (1H, br. s, Ar*H*), 6.59 (1H, dd, *J* = 8.8, 2.9, Ar*H*), 6.65 (1H, br. d, *J* = 9.2, Ar*H*), 6.90 (1H, dd, *J* = 8.8, 2.9, Ar*H*), 6.97-7.06 (3H, m, Ar*H*), 7.21-7.28 (4H, m, Ar*H*), 7.28-7.32 (1H, m, Ar*H*), 7.36 (1H, d, *J* = 7.5, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -67.5; ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.2 (Ar*C*H_3), 37.4 (Ph*C*H_2), 55.5 (O*C*H_3), 59.8 (*C*HN), 90.5 (*C*HNO_2), 113.8 (*Ar*H), 114.0 (*Ar*H), 116.2 (1C, q, *J* = 289.1), 126.2 (*Ar*H), 127.0 (*Ar*), 127.8 (*Ar*H), 128.7 (*Ar*H), 128.8 (*Ar*H), 129.1 (*Ar*H), 129.5 (*Ar*H), 131.2 (*Ar*H), 131.3 (*Ar*), 131.7 (*Ar*H), 132.9 (*Ar*H), 134.8 (*Ar*), 138.6 (*Ar*), 157.5 (1C, q, *J* = 35.8, *C*=O), 160.3 (*Ar*O); *m/z* (ESI^+) 495 (17, M+Na), 473 (3, M+H), 426 (30, M-NO_2); HRMS $C_{25}H_{23}F_3N_2O_4Na^+$ calcd. 495.1508, found 495.1489.

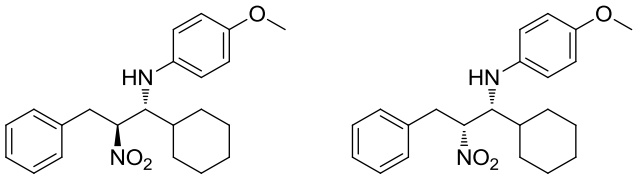
2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((2*R*,3*S*)-2-nitro-1-phenyloctan-3-yl) acetamide 239ai



When prepared by general procedure M. Nitroalkene **84a** (75 mg, 0.50 mmol) afforded after purification by column chromatography (10% Me_2CO/pet. ether) *β*-nitrotrifluoroacetamide **239ai** (190 mg, 0.41 mmol, 84% yield) as a yellow oil; IR

υ_{max} 2931 (C-H), 2861 (C-H), 1701 (C=O), 1556 (N-O), 1511, 1255, 1209, 1183, 1157 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 7.0, *CH*$_3$CH$_2$), 1.20-1.35 (4H, m, Me(C*H*$_2$)$_2$), 1.40-1.50 (3H, m, C*H*$_2$), 1.65 (1H, br. s, ^{n}BuC*H*$_2$), 3.30-3.40 (2H, m, PhC*H*$_2$), 3.88 (3H, s, OC*H*$_3$), 4.87 (1H, br s, C*H*NO_2), 4.97 (1H, br. s, C*H*N), 6.96-7.01 (2H, m, Ar*H*), 7.14 (2H, d, *J* = 7.0, Ar*H*), 7.19 (2H, d, *J* = 7.0, Ar*H*), 7.26-7.29 (1H, m, Ar*H*), 7.30-7.33 (2H, m, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -67.4 (s, C*F*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.1 (*C*H_3), 22.5 (Me*C*H_2), 26.1 (Et*C*H_2), 28.2 (^{n}Pr*C*H_2), 31.3 (*C*H_2), 37.8 (*C*H_2), 55.7 (O*C*H_3), 61.1 (*C*HN), 91.5 (*C*HNO_2), 114.7 (*Ar*H), 114.9 (*Ar*H), 116.3 (1C, q, *J* = 288.4, *C*F_3), 127.6 (*Ar*), 127.9 (*Ar*H), 128.6 (*Ar*H), 129.2 (*Ar*H), 130.3 (*Ar*H), 131.1 (*Ar*H), 134.7 (*Ar*), 158.7 (1C, q, *J* = 36.2, *C*=O), 160.6 (*Ar*O); *m/z* (EI) 452 (84, M), 406 (13, M-NO_2); HRMS $C_{23}H_{27}F_3N_2O_4$ calcd. 452.1917, found 452.1921. **When prepared enantioenriched**. To a mixture containing imine **30i** (0.200 mmol), nitroalkene **84a** (0.400 mmol) and Hantzsch ester **254** (0.400 mmol) in toluene (1.5 mL) at room temperature was added a solution of catalyst **272** (0.020 mmol, 0.2 M in toluene) and the reaction was stirred until reaction complete as monitored by ^1H NMR (1 h). Once reaction complete, trifluoroacetic anhydride (1.0 mmol), followed by pyridine (1.0 mmol) were added and the solution was stirred for 2 h at rt. After this time, 2.0 M HCl (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phases were then washed with sat. aq. $NaHCO_3$ 10 mL) and sat. brine (10 mL). The organic phase was then dried ($MgSO_4$) and the excess solvents were removed *in vacuo* to afford crude *β*-nitrotrifluoroacetamide **239ai** which was purified by column chromatography (4% Me_2CO/pet. ether and 40% CH_2Cl_2/pet. ether) to give **239ai** (53 mg, 0.117 mmol, 59% yield) as a yellow oil; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 99:1, flow rate = 1 mL/min, *λ* = 254 nm): retention time t_r (major) = 10.2 min, t_r (minor) = 15.9 min, shows 73% *ee*; $[\alpha]_D^{25}$ = -39.5 ^{o} (c = 1.10, $CHCl_3$).

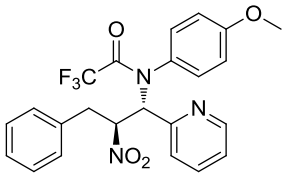
_N_-((1_S_*,2_R_*)-1-Cyclohexyl-2-nitro-3-phenylpropyl)-4-methoxyaniline and _N_-((1_S_*,2_S_*)-1-Cyclohexyl-2-nitro-3-phenylpropyl)-4-methoxyaniline 237aj



To a solution of nitroalkene **84a** (75 mg, 0.50 mmol) in CH_2Cl_2 (3 mL) was added Superhydride™ (0.55 mmol, 1.0 M in THF). The suspension was then stirred for 30 min at rt before cooling to –78 °C over 30 min. A solution of imine **30** (0.55 mmol) in CH_2Cl_2 (3 mL) was then added *via* cannula and the mixture stirred at -78 °C for 10 min. A solution of TFA (0.60 mmol) was added and the reaction was stirred for 1 h at –78 °C. The reaction was then quenched with sat. aq. NH_4Cl 5 mL) and diluted with Et_2O (10 mL). The organic phase was washed with sat. brine (5 mL) and dried ($MgSO_4$). The excess solvents were then removed *in vacuo* to afford crude *β*-nitroamine **237aj** which was purified by column chromatography (10% EtOAc/pet. ether) to first elute *β*-nitrotrifluoroacetamide **237aj major** (*anti*) (107 mg, 0.29 mmol, 58% yield) as a yellow oil; IR υ_{max} 3405 (N-H), 2927 (C-H), 2853 (C-H), 1545 (N-O), 1509, 1234 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.00-1.20 (2H, m, *Cy*), 1.20-1.30 (3H, m, *Cy*), 1.50-1.60 (1H, m *Cy*), 1.60 (1H, br. d, *J* = 9.0, *Cy*), 1.67 (1H, br. d, *J* = 13.2, *Cy*), 1.73 (1H, br. d, *J* = 10.2, *Cy*), 1.78 (1H br. d, *J* = 13.2, *Cy*), 1.85 (1H, br. d, *J* = 12.6, *Cy*), 3.26-3.32 (2H, m, PhC*H*$_2$), 3.41 (1H, d, *J* = 10.2, N*H*), 3.80 (3H, s, OC*H*$_3$), 3.82 (1H, m, CyC*H*N), 4.81 (1H, ddd, *J* = 9.4, 7.8, 4.8, C*H*NO_2), 6.61-6.64 (2H, m, Ar*H*), 6.77-6.80 (2H, m, Ar*H*), 7.13 (2H, d, *J* = 7.2, Ar*H*), 7.22-7.25 (1H, m, Ar*H*), 7.28 (2H, t, *J* = 7.2, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 26.0 (*C*H_2), 26.2 (*C*H_2), 26.3 (*C*H_2), 26.9 (*C*H_2), 31.2 (*C*H_2), 36.6 (Ph*C*H_2), 40.6 (*C*H), 55.9 (O*C*H_3), 62.1 (*C*HN), 91.7 (*C*HNO_2), 114.5 (*Ar*H), 115.2 (*Ar*H), 127.4 (*Ar*H), 128.8 (*Ar*H), 128.9 (*Ar*H), 136.3(*Ar*), 142.0 (*Ar*), 152.6 (*Ar*O); *m/z* (EI) 368 (8, M**)**, 239 (52), 218 (100); HRMS $C_{22}H_{28}N_2O_3$ calcd. 368.2094, found 368.2089; and then elute **237aj minor** (*syn*) (55 mg, 0.15 mmol, 30% yield) as a yellow oil; IR υ_{max} 3395 (N-H), 2925 (C-H), 2853 (C-H), 1547 (N-O), 1510, 1232 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.00-1.30 (5H, m, *Cy*), 1.50-1.60 (1H, m, *Cy*), 1.68 (1H, br. d, *J* = 12.0, *Cy*), 1.76 (2H, br. d, *J* = 12.8, *Cy*), 1.86 (2H, br. s, *Cy*), 3.16 (1H, dd, *J* =

14.4, 8.4, PhCH_2), 3.40 (1H, dd, *J* = 14.0, 8.0, PhCH_2), 3.51 (1H, m, C*H*N), 3.78 (3H, s, OCH_3), 3.91 (1H, d, N*H*), 5.08 (1H, ddd, *J* = 9.1, 5.5, 4.9, C*H*NO_2), 6.56-6.61 (2H, m, Ar*H*), 6.77-6.81 (2H, m, Ar*H*), 7.11-7.13 (2H, m, Ar*H*), 7.27-7.33 (3H, m, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 26.0 (*C*H_2), 26.1 (*C*H_2), 26.2 (*C*H_2), 29.2 (*C*H_2), 30.7 (*C*H_2), 37.6 (Ph*C*H_2), 41.6 (*C*H), 55.8 (O*C*H_3), 60.8 (*C*HN), 91.0 (*C*HNO_2), 114.1 (*Ar*H), 115.0 (*Ar*H), 127.4 (*Ar*H), 128.8 (*Ar*H), 128.9 (*Ar*H), 135.7 (*Ar*), 142.5 (*Ar*), 152.2 (*Ar*O); *m/z* (EI) 368 (33, M**)**, 239 (23), 218 (47); HRMS $C_{22}H_{28}N_2O_3$ calcd. 368.2094, found 368.2086.

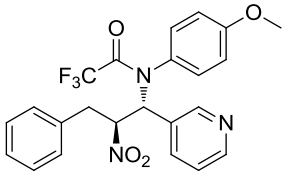
2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R*,2*R*)-2-nitro-3-phenyl-1-(pyridin-2-yl)propyl)acetamide 239ak



When prepared by general procedure M. Nitroalkene **84a** (75 mg, 0.50 mmol) afforded after purification by column chromatography (20% EtOAc/pet. ether) *β*-nitrotrifluoroacetamide **239ak** (138 mg, 0.30 mmol, 60% yield) as an off-white solid; mp 109-112 ^{o}C; IR υ_{max} 2919 (C-H), 1698 (C=O), 1555 (N-O), 1510, 1253, 1207, 1182, 1152 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.41 (1H, dd, *J* = 14.4, 10.8, PhCH_2), 3.60 (1H, dd, *J* = 14.4, 3.0, PhCH_2), 3.80 (3H, s, OCH_3), 5.63 (1H, apt. td, *J* = 10.8, 3.0, C*H*NO_2), 6.08 (1H, d, *J* = 7.2, Ar*H*), 6.59 (2H, d, *J* = 10.8, C*H*N, Ar*H*), 6.94 (1H, d, *J* = 7.2, Ar*H*), 7.19-7.24 (4H, m, Ar*H*), 7.28-7.32 (1H, m, Ar*H*), 7.35 (2H, t, *J* = 6.6, Ar*H*), 7.48 (1H, d, *J* = 7.8, Ar*H*), 7.71 (1H, td, *J* = 7.8, 1.8, Ar*H*), 8.31 (1H, d, *J* = 4.8 Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -67.3 (3F, s, CF_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.1 (Ph*C*H_2), 55.6 (O*C*H_3), 62.6 (*C*HN), 87.4 (*C*HNO_2), 114.1 (*Ar*H), 114.5 (*Ar*H), 116.4 (1C, q, *J* = 289.0, F_3C), 124.1 (*Ar*H), 124.6 (*Ar*H), 127.1 (*Ar*H), 128.0 (*Ar*H), 128.8 (*Ar*H), 129.1 (*Ar*H), 130.3 (*Ar*H), 131.6 (*Ar*H), 134.6 (*Ar*), 137.4 (*Ar*), 149.1 (*Ar*H), 153.7 (*Ar*), 158.4 (1C, q, *J* = 35.9, *C*=O), 160.5 (*Ar*O); *m/z* (ESI$^+$) 460 (100, M+H), 413 (95, M-NO_2); HRMS $C_{23}H_{20}F_3N_3O_4H^+$ calcd. 460.1491, found 460.1484; anal. calcd. for $C_{23}H_{20}F_3N_3O_4$: C, 60.13; H, 4.39; N, 9.15; found C, 60.19; H, 4.30; N, 9.14. **When prepared by general procedure O**. Imine **30k** (0.200 mmol) afforded, after purification by column chromatography (40% EtOAc/pet. ether and 25% Me_2CO/pet. ether), **239ak** (70 mg, 0.152 mmol, 76%

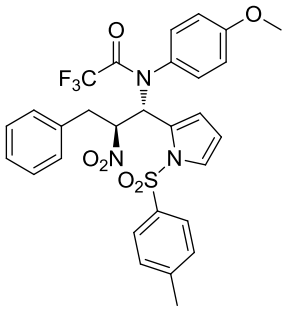
yield) as a white solid; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 90:10, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 10.4 min, t_r (minor) = 18.3 min, shows 96% *ee*; mp 94-95 ^oC; $[\alpha]_D^{25}$ = -55.5 ^{o} (c = 0.99, $CHCl_3$).

2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S,2*R**)-2-nitro-3-phenyl-1-(pyridin-3-yl)propyl)acetamide 239al**



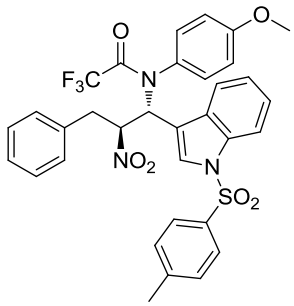
When prepared by general procedure M. Nitroalkene **84a** (75 mg, 0.50 mmol) afforded after purification by column chromatography (30% EtOAc/pet. ether) *β*-nitrotrifluoroacetamide **239al** (183 mg, 0.40 mmol, 80% yield) as an off-white solid; mp 147-150 ^oC; IR υ_{max} 3032 (C-H), 2970 (C-H), 1700 (C=O), 1557 (N-O), 1511, 1255, 1211, 1182, 1168 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.47 (1H, dd, *J* = 14.5, 11.1, PhC*H*$_2$), 3.55 (1H, dd, *J* = 14.5, 3.0, PhC*H*$_2$), 3.83 (3H, s, OC*H*$_3$), 5.68 (1H, br. s, C*H*NO_2), 5.95 (1H, br. s, C*H*N), 6.53 (1H, br. s, Ar*H*), 6.79 (1H, dd, *J* = 8.8, 2.6, Ar*H*), 6.95 (1H, dd, *J* = 8.7, 2.8, Ar*H*), 7.03 (1H, d, *J* = 7.1, Ar*H*), 7.20-7.24 (3H, m, Ar*H*), 7.31 (1H, m, Ar*H*), 7.36 (2H, m, Ar*H*), 7.53 (1H, d, *J* = 7.0, Ar*H*), 8.34 (1H, d, *J* = 1.8, Ar*H*), 8.59 (1H, dd, *J* = 4.8, 1.2, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -67.8 (3F, s, C*F*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.2 (Ph*C*H_2), 55.7 (O*C*H_3), 63.9 (*C*HN), 89.5 (*C*HNO_2), 114.6 (*Ar*H), 115.0 (*Ar*H), 116.1 (1C, q, *J* = 289.0, *C*F_3), 123.7 (*Ar*H), 128.0 (*Ar*), 128.2 (*Ar*H), 128.7 (*Ar*H), 129.1 (*Ar*), 129.3 (*Ar*H), 130.2 (*Ar*H), 131.8 (*Ar*H), 134.1 (*Ar*), 136.7 (*Ar*H), 150.6 (*Ar*H), 151.2 (*Ar*H), 158.3 (1C, q, *J* = 36.2, *C*=O), 160.8 (*Ar*O); *m/z* (EI) 459 (15, M**)**, 413 (7, M-NO_2); HRMS $C_{23}H_{20}N_3F_3O_4$ calcd. 459.1400, found 459.1408; anal. calcd. for $C_{23}H_{20}F_3N_3O_4$: C, 60.13; H, 4.39; N, 9.15; found C, 59.80; H, 4.33; N, 9.06.

2,2,2-Trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*R,2*R**)-2-nitro-3-phenyl-1-(1-tosyl-1*H*-pyrrol-2-yl)propyl)acetamide 239ao**



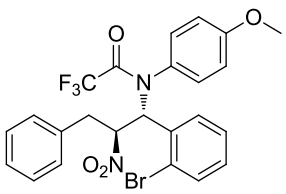
When prepared by general procedure M. Nitroalkene **84a** (75 mg, 0.50 mmol) afforded after purification by column chromatography (10% EtOAc/pet. ether) *β*-nitrotrifluoroacetamide **239ao** (225 mg, 0.374 mmol, 75% yield) as a yellow solid; mp 192-196 ^{o}C; IR υ_{max} 2938 (C-H), 1702 (C=O), 1557 (N-O), 1511, 1370, 1179, 1154 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.47 (3H, s, ArC*H*$_3$), 3.34 (1H, dd, *J* = 14.4, 10.8, PhC*H*$_2$), 3.40 (1H, dd, *J* = 15.0, 4.2, PhC*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 4.96 (1H, apt. td, *J* = 10.8, 4.2, C*H*NO$_2$), 5.74 (1H, dd, *J* = 3.6, 1.2, Ar*H*), 5.97 (1H, t, *J* = 3.6, Ar*H*), 6.51 (1H, dd, *J* = 8.9, 2.2, Ar*H*), 6.64 (1H, dd, *J* = 8.9, 2.9, Ar*H*), 6.72 (1H, d, *J* = 11.0, C*H*N), 6.90 (1H, dd, *J* = 8.6, 2.9, Ar*H*), 7.02 (1H, dd, *J* = 8.6, 2.6, Ar*H*), 7.14 (2H, d, *J* = 7.0, Ar*H*), 7.27-7.35 (3H, m, Ar*H*), 7.40-7.43 (3H, m, Ar*H*), 7.86 (2H, d, *J* = 8.4, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -68.0 (3F, s, C*F*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.9 (Ar*C*H$_3$), 38.0 (Ph*C*H$_2$), 54.8 (*C*HN), 55.6 (O*C*H$_3$), 90.0 (*C*HNO$_2$), 111.0 (*Ar*H), 113.8 (*Ar*H), 114.4 (*Ar*H), 116.3 (1C, q, *J* = 288.6, *C*F$_3$), 117.9 (*Ar*H), 124.5 (*Ar*), 124.7 (*Ar*H), 127.7 (*Ar*), 127.7 (*Ar*H), 128.0 (*Ar*H), 128.6 (*Ar*H), 129.2 (*Ar*H), 129.7 (*Ar*H), 130.4 (*Ar*H), 132.0 (*Ar*H), 134.7 (*Ar*), 134.8 (*Ar*), 146.1 (*Ar*), 158.2 (1C, q, *J* = 36.2, *C*=O), 160.4 (*Ar*O); *m/z* (CI) 602 (4, M+H**)**, 555 (6, M-NO$_2$), 383 (100, M-C$_9$H$_7$F$_3$NO$_2$); HRMS $C_{29}H_{26}N_3F_3O_6SH^+$ calcd. 602.1573, found 602.1586; anal. calcd. for $C_{29}H_{26}N_3F_3O_6S$: C, 57.90; H, 4.36; N, 6.98; found C, 57.82; H, 4.28; N, 6.95.

2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S,2*R**)-2-nitro-3-phenyl-1-(1-tosyl-1*H*-indol-3-yl)propyl)acetamide 239aq**



When prepared by general procedure M. Nitroalkene **84a** (75 mg, 0.50 mmol) afforded after purification by column chromatography (10% EtOAc/pet. ether) *β*-nitrotrifluoroacetamide **239aq** (208 mg, 0.32 mmol, 64% yield) as an off-white solid; mp 90-95 ^{o}C; IR υ_{max} 2934 (C-H), 1698 (C=O), 1557 (N-O), 1511, 1448, 1371, 1210 1171 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.31 (3H, s, ArC*H*$_3$), 3.51 (1H, dd, *J* = 14.5, 11.5, PhC*H*$_2$), 3.61 (1H, dd, *J* = 14.6, 2.8, PhC*H*$_2$), 3.84 (3H, s, OC*H*$_3$), 5.33 (1H, br. s, C*H*NO$_2$), 6.09 (1H, br. s, C*H*N), 6.54 (1H, d, *J* = 7.3, Ar*H*), 6.68 (1H, br. s, Ar*H*), 6.97 (1H, dd, *J* = 8.6, 2.2, Ar*H*), 7.13-7.22 (4H, m, Ar*H*), 7.24 (2H, d, *J* = 7.2, Ar*H*), 7.28-7.40 (5H, m, Ar*H*), 7.51 (1H, br. s, Ar*H*), 7.57 (2H, d, *J* = 8.3, Ar*H*), 7.95 (1H, d, *J* = 8.3, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$), δ -67.61 (3F, s, C*F*$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.7 (Ar*C*H$_3$), 38.0 (Ph*C*H$_2$), 54.9 (*C*HN), 55.7 (O*C*H$_3$), 89.8 (*C*HNO$_2$), 114.0 (*Ar*H), 114.2 (*Ar*H), 114.7 (*Ar*H), 114.8 (*Ar*), 116.2 (1C, q, *J* = 288.5, *C*F$_3$), 119.3 (*Ar*H), 124.4 (*Ar*H), 125.9 (*Ar*H), 126.6 (*Ar*H), 127.0 (*Ar*H), 128.2 (*Ar*H), 128.6 (*Ar*H), 129.2 (*Ar*), 129.3 (*Ar*H), 129.8 (*Ar*H), 130.1 (*Ar*H), 132.0 (*Ar*H), 134.2 (*Ar*), 134.3 (*Ar*), 134.6 (*Ar*), 145.6 (*Ar*), 158.5 (1C, q, *J* = 36.2, *C*=O), 160.7 (*Ar*O); *m/z* (ESI$^+$), 674 (21, M+Na), 605 (16, M-NO$_2$); HRMS $C_{33}H_{28}F_3N_3O_6SNa^+$ calcd. 674.1549, found 674.1558.

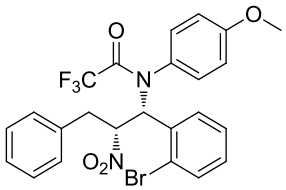
***N*-((1*R*,2*S*)-1-(2-Bromophenyl)-2-nitro-3-phenylpropyl)-2,2,2-trifluoro-*N*-(4-methoxyphenyl)acetamide 239ar**



Prepared by general procedure O. Imine **30r** (0.200 mmol) afforded, after purification by column chromatography (10% EtOAc/pet. ether and 50% CH_2Cl_2/pet.

ether), major diastereomer **239ar** (75 mg, 0.140 mmol, 70% yield) as a white solid; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 97.5:2.5, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 12.6 min, t_r (minor) = 15.7 min, shows 92% *ee*; mp 158-160 ^oC; $[\alpha]_D^{25}$ = -61.4 ^{o} (c = 1.04, $CHCl_3$); IR υ_{max} 2935 (C-H), 1702 (C=O), 1556 (N-O), 1510, 1256, 1208, 1181 cm^1; ^1H NMR (600 MHz, $CDCl_3$) δ 3.55 (1H, dd, *J* = 14.7, 2.8, PhCH_2), 3.60 (1H, dd, *J* = 15.2, 10.7, PhCH_2), 3.80 (3H, s, OCH_3), 5.48 (1H, apt. td, *J* = 10.7, 3.4, C*H*NO_2), 6.27 (1H, br. d, *J* = 8.3, Ar*H*), 6.58 (1H, dd, *J* = 8.8, 2.7, Ar*H*), 6.80 (1H, br. d, *J* = 11.1, C*H*N), 6.83 (1H, br. d, *J* = 7.7, Ar*H*), 6.92 (1H, dd, *J* = 8.8, 2.9, Ar*H*), 7.02 (1H, t, *J* = 7.6, Ar*H*), 7.05 (1H, dd, *J* = 8.7, 1.7, Ar*H*), 7.15 (1H, td, *J* = 7.5, 1.1, Ar*H*), 7.25 (2H, d, *J* = 7.2, Ar*H*), 7.32 (1H, t, *J* = 7.3, Ar*H*), 7.37 (2H, t, *J* = 7.3, Ar*H*), 7.62 (1H, d, *J* = 8.1, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -67.6; ^{13}C NMR (151 MHz, $CDCl_3$) δ 38.2 (Ph*C*H_2), 55.6 (O*C*H_3), 62.2 (*C*HN), 89.7 (*C*HNO_2), 113.9 (*Ar*H), 114.5 (*Ar*H), 116.4 (1C, q, *J* = 288.5, *C*F_3), 126.1 (*Ar*), 127.2 (*Ar*), 127.4 (*Ar*H), 128.1 (*Ar*H), 128.7 (*Ar*H), 129.3 (*Ar*H), 129.8 (*Ar*H), 130.1 (*Ar*H), 131.0 (*Ar*H), 132.3 (*Ar*H), 132.4 (*Ar*), 133.8 (*Ar*H), 134.7 (*Ar*), 157.9 (1C, q, *J* = 35.8, *C*=O), 160.5 (*Ar*O); *m/z* (CI) 538 (17, ^{81}M), 536 (17, ^{79}M), 492 (26, ^{81} M-NO_2), 490 (25, ^{79}M-NO_2); HRMS $C_{24}H_{20}BrF_3N_2O_4$ calcd. 536.0559, found 536.0554.

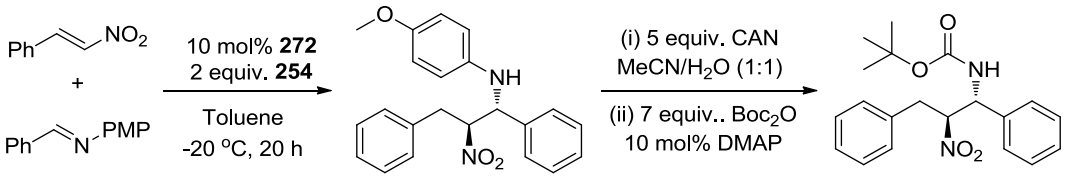
_N_-((1_R_,2_R_)-1-(2-Bromophenyl)-2-nitro-3-phenylpropyl)-2,2,2-trifluoro-_N_-(4-methoxyphenyl)acetamide 239ar *syn*



Prepared by general procedure O. Imine **30r** (0.200 mmol) afforded, after purification by column chromatography (10% EtOAc/pet. ether and 50% CH_2Cl_2/pet. ether), minor diastereomer **239ar *syn*** (10 mg, 0.019 mmol, 9% yield) as a white solid; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 90:10, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 11.3 min, t_r (minor) = 17.4 min, shows 10% *ee*; mp 134-135 ^oC; IR υ_{max} 2843 (C-H), 1706 (C=O), 1559 (N-O), 1511, 1206, 1183 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) δ 2.79 (1H, br. d, *J* = 13.6, PhCH_2), 3.26 (1H, dd, *J* = 14.8, 11.3, PhCH_2), 3.83 (3H, s, OCH_3), 5.84 (1H, br. t, *J* = 9.8, C*H*NO_2), 6.56 (2H, br. d, *J* = 8.3, C*H*N, Ar*H*), 6.72 (1 H, dd, *J* = 8.8, 3.0, Ar*H*), 6.87

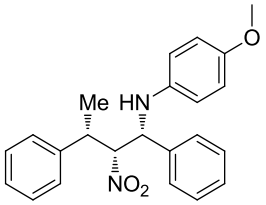
(1H, dd, *J* = 8.8, 3.0, Ar*H*), 7.02-7.09 (2H, m, Ar*H*), 7.10-7.28 (7H, m, Ar*H*), 7.71 (1H, d, *J* = 7.5, Ar*H*); ^{19}F NMR (300 MHz, $CDCl_3$) δ -67.7; ^{13}C NMR (151 MHz, $CDCl_3$) δ 37.3 (Ph*C*H_2), 55.6 (O*C*H_3), 65.2 (*C*HN), 89.9 (*C*HNO_2), 113.9 (*Ar*H), 114.5 (*Ar*H), 116.1 (1C, q, *J* = 289.1, *C*F_3), 126.4 (*Ar*), 127.8 (*Ar*H), 128.0 (*Ar*H), 128.6 (*Ar*H), 129.1 (*Ar*H), 130.5 (*Ar*H), 131.0 (*Ar*H), 131.1 (*Ar*H), 131.6 (*Ar*H), 133.3 (*Ar*), 134.1 (*Ar*H), 134.7 (*Ar*), 157.5 (1C, q, *J* = 35.8, *C*=O), 160.3 (O*C*H_3); *m/z* (ESI^+) 539 (5, ^{81}M+H), 537 (6, ^{79}M+H), 492 (100, ^{81}M-NO_2), 490 (98, ^{79}M-NO_2); HRMS $C_{24}H_{20}BrF_3N_2O_4$ calcd. 537.0637, found 537.0631.

tert-Butyl ((1*R*,2*S*)-2-nitro-1,3-diphenylpropyl)carbamate 257



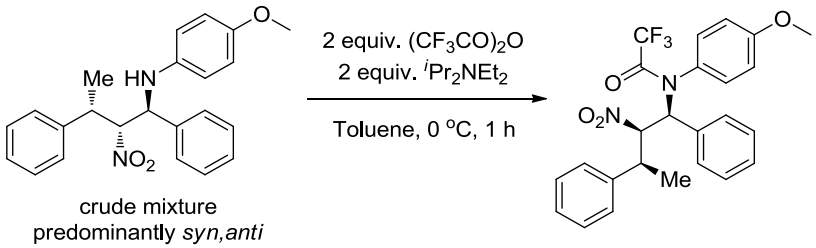
To a mixture containing imine **30a** (84 mg, 0.40 mmol), nitroalkene **84a** (120 mg, 0.80 mmol) and Hantzsch ester **254** (248 mg, 0.80 mmol) in toluene (3 mL) cooled to -20 ^{o}C (Cryobath) was added a solution of catalyst **272** (200 μL, 0.04 mmol, 0.2 M in toluene) and the reaction was stirred for 20 h. The excess solvent was removed *in vacuo* and the crude *β*-nitroamine was dissolved in MeCN (8 mL) and added to a pre-cooled solution of ceric ammonium nitrate (1.10 g, 2.00 mmol) in water (8 mL) at 0 ^{o}C. The reaction was stirred for 1 h at this temperature to give a black mixture and then di-*tert*-butyl dicarbonate (611 mg, 2.80 mmol) and 4-dimethylpyridine (5 mg, 0.04 mmol) were added and the reaction was allowed to warm to rt and stirred for 16 h. The excess solvent was then removed *in vacuo* and the resultant residue was diluted with EtOAc (40 mL). This mixture was then washed with sat. aq. $NaHCO_3$ 2 x 20 mL), dried ($MgSO_4$) and the excess solvent was removed *in vacuo* to give crude **257** which was purified by column chromatography (20% EtOAc/pet. ether) to give **257** (56 mg, 0.16 mmol, 39% yield) as a white solid; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 90:10, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 11.0 min, t_r (minor) = 12.7 min, shows 94% *ee*; mp 179-180 ^{o}C; $[\alpha]_D^{25}$ = -46.0 ^{o} (c = 0.90, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.47 (9H, s, C(CH_3)$_3$), 3.18 (1H, dd, *J* = 14.8, 3.52, PhCH_2), 3.32 (1H, dd, *J* = 14.6, 10.56, PhCH_2), 5.13 (1H, br. s, C*H*NO_2), 5.26 (2H, br. s, N*H*, C*H*N), 7.16 (2H, d, *J* = 6.8, Ar*H*), 7.23-7.33 (5H, m, Ar*H*), 7.36-7.43 (3H, m, Ar*H*); ^{1}H NMR data are consistent with literature data.[36]

4-Methoxy-*N*-((1*R*,2*R*,3*S*)-2-nitro-1,3-diphenylbutyl)aniline 287a



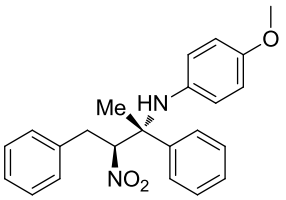
To a solution of *β*-nitro-*α*-methylstyrene **286** (64 mg, 0.400 mmol) in toluene (2 mL) at rt was added Hantzsch ester **254** (124 mg, 0.400 mmol) and *N*-PMP phenyl imine **30a** (42 mg, 0.200 mmol) and the reaction was stirred at rt for 5min after which a solution of thiourea **272** (0.2 M in toluene, 100 μL, 0.020 mmol) was added and the reaction was stirred at rt for 16 h. The excess solvent was removed *in vacuo* to give crude product which was then purified by column chromatography (10% Me_2CO/pet. ether, then 10% EtOAc/pet. ether) to give **287a** (28 mg, 0.074 mmol, 37% yield) as a white foam; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 99:1, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 12.4 min, t_r (minor) = 14.2 min, shows 84% *ee*; $[\alpha]_D^{16}$ = +9.2 ^{o} (c = 0.68, CH_2Cl_2); ^{1}H NMR$_{syn,syn}$ (600 MHz, $CDCl_3$) δ 1.37 (3H, d, *J* = 7.0, C*H*$_3$), 3.67 (3H, s, OC*H*$_3$), 3.87 (1H, dq, *J* = 10.9, 6.8, PhC*H*Me), 4.25 (1H, dd, *J* = 10.4, 3.6, C*H*N), 4.88 (1H, dd, *J* = 10.9, 3.8, C*H*NO_2), 5.10 (1H, d, *J* = 10.5, N*H*), 6.29-6.34 (2H, m, Ar*H*), 6.62-6.66 (2H, m, Ar*H*), 7.06-7.09 (2H, m, Ar*H*), 7.19-7.22 (1H, m, Ar*H*), 7.23-7.29 (4H, m, Ar*H*), 7.29-7.35 (3H, m, Ar*H*); ^{1}H NMR data consistent with literature data.[53] Minor diastereomers unstable to purification but partially visible from ^{1}H NMR data; ^{1}H NMR$_{syn,anti}$ (600 MHz, $CDCl_3$) δ 3.60 (1H, apt. t, *J* = 7.0, PhC*H*Me), 4.18 (1H, d, *J* = 9.0, N*H*), 4.83 (1H, dd, *J* = 8.7, 6.6), 6.51-6.55 (2H, m, Ar*H*) other peaks not visible; ^{1}H NMR$_{anti,syn}$ (600 MHz, $CDCl_3$) δ 3.43 (1H, dq, *J* = 10.0, 7.0, PhC*H*Me) 4.08 (1H, d, *J* = 8.3, N*H*), 4.64 (1H, dd, *J* = 7.9, 4.9) other peaks not visible.

2,2,2-trifluoro-*N*-(4-methoxyphenyl)-*N*-((1*S*,2*R*,3*S*)-2-nitro-1,3-diphenylbutyl)acetamide



To confirm stereochemistry of **287b** a solution of crude reaction mixture of **287** (after 30 min reaction time) diastereomerically enriched with *syn,syn* **287b** in toluene (2 mL) at 0 ^{o}C was added trifluoroacetic anhydride (0.40 mmol) and $^{i}Pr_2Net$ (0.40 mmol) and the reaction was allowed to warm to rt and stirred for 1 h. After this time, 2.0 M HCl (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic phases were washed with sat. aq. $NaHCO_3$ 10 mL) and sat. brine (10 mL). The organic phase was then dried ($MgSO_4$) and the excess solvents were removed *in vacuo* to afford crude *β*-nitrotrifluoroacetamide; ^{1}H $NMR_{syn,anti}$ (600 MHz, $CDCl_3$) δ 1.61 (3H, d, *J* = 7.2, C*H*$_3$), 3.66 (1H, qd, *J* = 7.9, 4.5, C*H*Me), 3.80 (3H, s, OMe), 5.68 (1H, dd, *J* = 10.8, 4.3, C*H*NO_2), 6.19 (1H, d, *J* = 10.6 C*H*N), 6.22-6.28 (1H, m, Ar*H*) remaining peaks could not be distinguished; ^{1}H NMR data are consistent with literature data.[53]

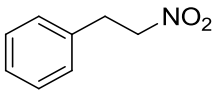
4-Methoxy-*N*-((2*R*,3*S*)-3-nitro-2,4-diphenylbutan-2-yl)aniline 292



To a mixture containing imine **291** (0.20 mmol), nitroalkene **84a** (0.40 mmol) and Hantzsch ester **254** (0.40 mmol) in toluene (1.5 mL) cooled to -20 ^{o}C (Cryobath) was added a solution of catalyst **272** (0.02 mmol, 0.2 M in toluene) and the reaction was stirred at this temperature. After a set time (16-24 h) the excess solvent was removed *in vacuo* to give crude product **292** which was analysed by ^{1}H NMR. ^{1}H NMR_{MAJOR} (400 MHz, $CDCl_3$) δ 2.94 (1H, dd, *J* = 15.1, 2.8, PhC*H*$_2$), 3.45 (1H, dd, *J* = 15.1, 11.8, PhC*H*$_2$), 3.73 (3H, s, OC*H*$_3$), 4.80 (1H, dd, *J* = 12.0, 2.8, C*H*NO_2), 6.45-6.50 (2H, m, Ar*H*), 6.66-6.71 (2H, m, Ar*H*) other signals could not be determined; ^{1}H NMR_{MINOR} (600 MHz, $CDCl_3$) δ 4.84 (1H, dd, *J* = 13.7, 8.1, C*H*NO_2), 6.28-6.33 (2H, m, Ar*H*), 6.56-6.60 (2H, m, Ar*H*) other signals could not be determined.

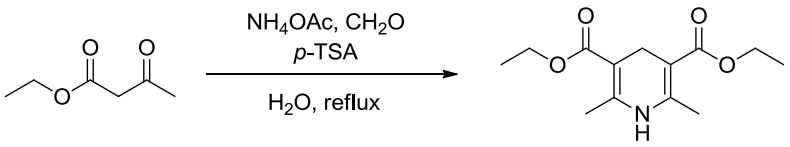
4.2.5 Miscellaneous compounds and total synthesis intermediates

(2-Nitroethyl)benzene 234



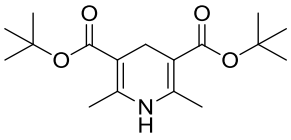
Superhydride™ (500 μL, 0.50 mmol, 1.0 M, in THF) was added to a yellow solution of *β*-nitrostyrene (75 mg, 0.50 mmol) in THF (3 mL) at 0 °C. After 30 min, 1.0 M HCl (2 mL) was added and the mixture was stirred vigorously for 15 min. The mixture was then extracted with Et_2O (2 x 10 mL) and the combined organics were washed with sat. brine (5 mL), dried ($MgSO_4$) and the excess solvent was removed *in vacuo* to leave crude **234** as a yellow oil. Purification by flash chromatography (5% EtOAc/pet. ether) afforded **234** (72 mg, 0.48 mmol, 95%) as a colourless oil; ^{1}H NMR ($CDCl_3$) δ 3.36 (2H, t, *J* = 7.4, C*H*$_2$Ar), 4.63 (2H, t, *J* = 7.4, C*H*$_2$NO$_2$), 7.24 (2H, m, Ar*H*), 7.32 (3H, m, Ar*H*). ^{1}H NMR data are consistent with literature data.[176]

Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate 255



Prepared according to literature procedure.[177] Ammonium acetate (20.0 mmol) gave crude **255** (2.30 g) as a yellow solid which was recrystallised (EtOH, 10 mL/g) to give **255** (1.53 g, 6.0 mmol, 60% yield) as a pale yellow solid; mp 188-190 °C (Lit.[178] 183-185 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (6H, t, *J* = 7.1, CH_2CH_3), 2.20 (6H, s, C*H*$_3$), 3.28 (2H, s, C*H*$_2$), 4.18 (4H, q, *J* = 7.1, C*H*$_2$CH$_3$), 5.11 (1H, br. s, N*H*); ^{1}H NMR data are consistent with literature data.

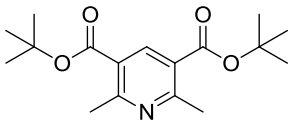
Di-*tert*-butyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate 254



To a mixture of ammonium acetate (6.17 g, 80.0 mmol) in EtOH (60 mL) was added *tert*-butylacetoacetate (6.5 mL, 40.0 mmol), formaldehyde (35 wt% in water, 1.6 mL, 20 mmol) and *para*-toluenesulfonic acid monohydrate (0.76 g, 4.0 mmol). The colourless mixture was heated at reflux (80 °C) for 1 h to give a yellow solution

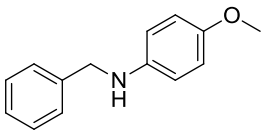
which was then allowed to cool to rt. After 5 min, water (50 mL) was added and a precipitate was formed upon cooling. The reaction was then cooled to 0 °C and filtered to give **254** (4.76 g, 15.4 mmol, 77% yield) as a pale yellow solid; mp 127-129 °C; IR υ_{max} 2978 (C-H), 1718 (C=O), 1369, 1267, 1157 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.47 (18H, s, C(C*H*$_3$)$_3$), 2.14 (6H, s, C*H*$_3$), 3.17 (2H, s, C*H*$_2$), 5.00 (1H, br. s, N*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 19.4 (*C*H$_3$), 25.5 (*C*H$_2$), 28.5 (C(*C*H$_3$)$_3$), 79.5 (*C*Me$_3$), 101.0 (*C*Me), 143.8 (*C*CO), 167.7 (*C*=O); *m/z* (CI) 309 (20, M), 308 (100, M-H); HRMS $C_{17}H_{27}NO_4$ calcd. 309.1940, found 309.1927.

Di-*tert*-butyl 2,6-dimethylpyridine-3,5-dicarboxylate 260



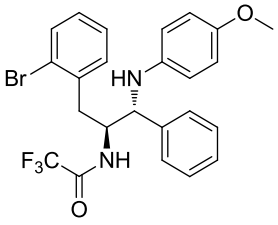
Formed as a by-product from **general procedures N and O** as a yellow solid; mp 88-90 °C (Lit.[179] 108-110 °C) ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.60 (18H, s, C(C*H*$_3$)$_3$), 2.80 (6H, s, C*H*$_3$), 8.52 (1H, s, Ar*H*); ^{1}H NMR data are consistent with literature data.[179]

***N*-Benzyl-4-methoxyaniline 264**



Formed as a by-product from **general procedures N and O** as a brown solid; mp 49-51 °C (Lit.[180] 50 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.72 (3H, s, OC*H*$_3$), 4.24 (2H, s, PhC*H*$_2$N), 6.52-6.60 (2H, m, Ar*H*), 6.77-6.75 (2H, m, Ar*H*), 7.22-7.35 (5H, m, Ar*H*). ^{1}H NMR data are consistent with literature data.[181]

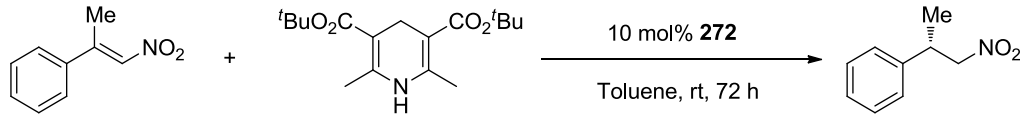
***N*-((1*R*,2*S*)-3-(2-Bromophenyl)-1-((4-methoxyphenyl)amino)-1-phenylpropan-2-yl)-2,2,2-trifluoroacetamide 276oa**



Prepared using a modified literature procedure.[127] To a solution of *β*-nitrotrifluoroacetamide **239oa** (0.80 g, 1.5 mmol) in EtOH (60 mL) and EtOAc (45

mL) pre-cooled to 0 °C was added 6.0 M HCl (62.5 mL, 375.0 mmol). To this white suspension was added portionwise Zn dust (7.35 g, 112.5 mmol) [CAUTION – gas evolution] over 30 min. The reaction was then allowed to warm to rt and stirred for 2 h 30, after which time water (120 mL) was added. The organics were then removed *in vacuo* and the resultant aqueous mixture was extracted with EtOAc (250 mL, then 50 mL). The combined organics were then washed with sat. aq. $NaHCO_3$ 2 x 100 mL) and with sat. brine (25 mL). The resultant organic phase was then dried (Na_2SO_4) and the excess solvent removed to give a pink oil. This residue was re-dissolved in EtOH (60 mL) and EtOAc (40 mL) and 6.0 M HCl (5 mL, 30.0 mmol) was added and the mixture was stirred at rt for 1 h. The organics were then removed *in vacuo* and the resultant residue was diluted with EtOAc (100 mL) and water (50 mL). The bi-phasic mixture was separated and the organic phase was washed with aqueous sat. aq. $NaHCO_3$ 100 mL), dried (Na_2SO_4) and the excess solvent was removed *in vacuo* to afford 1,2-diamine **276oa** (0.73 g, 1.4 mmol, 96% yield) as a pink solid; mp 112-113 °C; $[\alpha]_D^{25}$ = -34.7 ° (c = 0.945, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.82 (1H, dd, *J* = 13.9, 11.1, ArC*H*$_2$), 3.14 (1H, dd, *J* = 14.0, 3.7, ArC*H*$_2$), 3.69 (3H, s, OC*H*$_3$), 4.32 (1H, br. s, N*H*PMP), 4.69 (1H, d, *J* = 3.6, PhC*H*N), 4.74 (1H, m, CH_2C*H*N), 6.35 (1H, d, *J* = 8.8, N*H*CO), 6.54 (2H, d, *J* = 9.0, Ar*H*), 6.70 (2H, d, *J* = 8.8, Ar*H*), 7.07-7.12 (2H, m, Ar*H*), 7.19-7.23 (1H, m, Ar*H*), 7.31-7.35 (1H, m, Ar*H*), 7.38-7.42 (4H, m, Ar*H*), 7.49-7.53 (1H, m, Ar*H*). ^{1}H NMR data are consistent with literature data.[127]

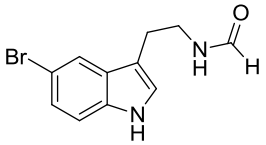
(*S*)-(1-Nitropropan-2-yl)benzene 288



To a solution of *β*-nitro-*α*-methylstyrene **286** (0.200 mmol) in toluene (0.5 mL) at rt was added Hantzsch ester **254** (62 mg, 0.200 mmol) and the reaction was stirred at rt for 5min after which a solution of thiourea **272** (0.2 M in toluene, 100 μL, 0.020 mmol) was added and the reaction was stirred at rt until complete as judged from ^{1}H NMR data (*ca.* 72 h). The excess solvent was then removed *in vacuo* to give the crude product which was purified by column chromatography (1-2% Et_2O/pet. ether) to give **288** (26 mg, 0.157 mmol, 79% yield) as a colourless oil; $[\alpha]_D^{25}$ = -48.7 ° (c = 0.855, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (3H, d, *J* = 7.0, C*H*$_3$), 3.61-3.71

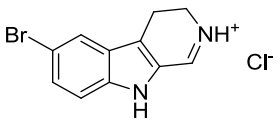
(1H, m, PhC*H*), 4.51 (1H, dd, *J* = 11.8, 8.2, CH_2NO_2), 4.58 (1H, dd, *J* = 12.0, 7.0, CH_2NO_2), 7.23-7.33 (3H, m, Ar*H*), 7.34-7.40 (2H, m, Ar*H*). ^{1}H NMR data are consistent with literature data.[119]

_N_-(2-(5-Bromo-1_H_-indol-3-yl)ethyl)formamide 305



Prepared using a modified literature procedure.[182] A mixture of 5-Bromotryptamine (570 mg, 2.39 mmol) in ethylformate (20 mL) was heated at reflux (56 ^{o}C) for 16 h and then cooled to rt. The excess solvent was then removed *in vacuo* to give crude **305** (645 mg, quantitative yield) as an off-white solid; mp 128-131 ^{o}C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.81 (2H, t, *J* = 7.2, ArCH_2), 3.35 (2H, apt. q, *J* = 6.6, CH_2NH), 7.17 (1H, dd, *J* = 8.6, 1.8, Ar*H*), 7.23 (1H, d, *J* = 1.9, Ar*H*), 7.31 (1H, d, *J* = 8.7, Ar*H*), 7.71 (1H, d, *J* = 1.7, Ar*H*), 8.02 (1H, s Ar*H*), 8.08 (1H, br. s, N*H*), 11.07 (1H, s, *H*C=O); ^{1}H NMR$_{ROTAMER}$ δ 7.22 (1H, d, *J* = 2.1), 7.74 (1H, d, *J* = 1.5), 7.80 (1H, d, *J* = 11.9) other peaks not visible; ^{13}C NMR (151 MHz, DMSO-d_6) δ 24.9 (*C*H_2), 38.0 (*C*H_2), 111.0 (*Ar*), 111.6 (*Ar*), 113.4 (*Ar*H), 120.6 (*Ar*H), 123.4 (*Ar*H), 124.6 (*Ar*H), 129.1 (*Ar*), 134.9 (*Ar*), 161.1 (O=*C*H); ^{13}C NMR$_{ROTAMER}$ (151 MHz, DMSO-d_6) δ 26.9 (*C*H_2), 41.8 (*C*H_2), 111.1 (*Ar*), 111.2 (*Ar*), 113.4 (*Ar*H), 120.7 (*Ar*H), 123.4 (*Ar*H), 124.9 (*Ar*H), 129.1 (*Ar*), 134.9 (*Ar*), 164.5 (O=*C*H); *m/z* (EI) 268 (14, ^{81}M), 266 (14, ^{79}M), 223 (86, ^{8}M-$NCOH_3$), 221 (87, ^{79}M-$NCOH_3$), 210 (96, ^{81}M-NC_2OH_4), 208 (100, ^{79}M-NC_2OH_4); HRMS $C_{11}H_{11}BrN_2O$ calcd. 266.0055, found 266.0050.

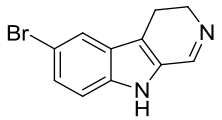
6-Bromo-4,9-dihydro-3_H_-pyrido[3,4-b]indol-2-ium chloride 304



Prepared using a modified literature procedure.[146] To a pre-cooled solution of $POCl_3$ (700 μL, 7.50 mmol) at 3 ^{o}C (ice-bath) was added portionwise over 30 min formamide **305** (200 mg, 0.75 mmol). After approximately 30 min at this temperature a thick yellow suspension formed which would no longer stir. To this mixture was added Et_2O (2 mL) and the reaction was left to warm to rt and stirred for 2 h or until reaction complete as judged by tlc analysis. The yellow suspension was then filtered and washed with more Et_2O to give acid salt of **304** (182 mg, 0.64

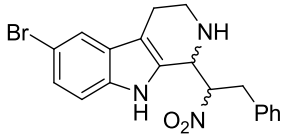
mmol, 85% yield) as a yellow HCl salt; ^{1}H NMR (600 MHz, DMSO-d_6) δ 3.25 (2H, t, *J* = 9.1, ArCH_2), 3.98 (2H, q, *J* = 9.0, CH_2N), 7.54 (1H, dd, *J* = 8.8, 1.7, Ar*H*), 7.57 (1H, dd, *J* = 8.8, 0.6, Ar*H*), 7.98-8.18 (1H, m, Ar*H*), 9.08 (1H, s, N=C*H*), 12.48 (1H, s, N*H*), 12.75 (1H, br. s, N*H*); ^{1}H NMR (151 MHz, DMSO-d_6) δ 18.4 (*C*H_2), 41.7 (*C*H_2), 113.8 (*Ar*), 115.7 (*Ar*H), 122.8 (*Ar*), 124.2 (*Ar*H), 125.3 (*Ar*), 126.1 (*Ar*), 130.9 (*Ar*H), 139.4 (*Ar*), 155.9 (H*C*=N).

6-Bromo-4,9-dihydro-3H-pyrido[3,4-b]indole 304



Prepared using a modified literature procedure.[146] The acid salt of **304** (182 mg, 0.64 mmol) was stirred vigorously in water (10 mL) until dissolved. The aqueous solution was then washed with Et_2O (10 mL) and basified with aqueous ammonia (30 wt%) to pH 10, giving a cloudy white mixture. This was then extracted with more Et_2O (3 x 10 mL), dried (Na_2SO_4) and filtered to give desired product **304** (149 mg, 0.60 mmol, 80% yield) as a yellow foam; IR υ_{max} 2924 (C-H), 1726 (C=N), 1596, 1549, 1438, 1380, 1358, 1172 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.86 (2H, t, *J* = 8.7, ArCH_2), 3.94 (2H, t, *J* = 7.9, CH_2N), 7.24 (1H, d, *J* = 8.8, Ar*H*), 7.35 (1H, dd, *J* = 8.7, 1.3, Ar*H*), 7.72 (1H, s, Ar*H*), 8.37 (1H, br. s, N=C*H*), 8.51 (1H, br. s, N*H*); too unstable to get clean carbon; *m/z* (EI) 250 (65, ^{81}M), 249 (100, ^{81}M-H), 248 (88, ^{79}M), 247 (94, ^{79}M-H); HRMS $C_{11}H_9BrN_2$ calcd. 247.9950, found 247.9938.

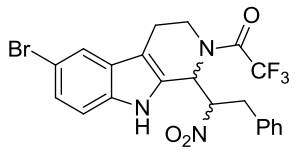
6-Bromo-1-(1-nitro-2-phenylethyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indole 303



To a solution of *β*-nitrostyrene **84a** (30 mg, 0.20 mmol) in CH_2Cl_2 (1.5 mL) was added Superhydride^{TM} (220 μL, 0.22 mmol, 1.0 M in THF). The suspension was then stirred for 30 min at rt before cooling to –78 °C over 30 min. A solution of imine **304** (44 mg, 0.18 mmol) in CH_2Cl_2 (3 mL) was added *via* cannula and the mixture stirred at -78 °C for 10 min. A solution of TFA (20 μL, 0.24 mmol) was added and the reaction was stirred for 1 h at –78 °C. The reaction was then quenched with sat. aq. NH_4Cl 10 mL) and diluted with Et_2O (20 mL). The organic phase was washed with

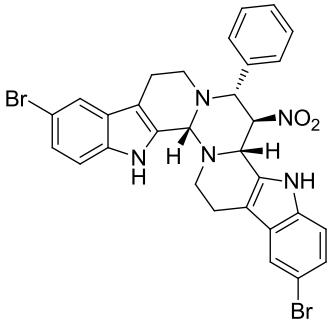
sat. brine (10 mL) and dried ($MgSO_4$). Solvents were removed *in vacuo* to afford crude *β*-nitroamine **303** as a yellow oil; ^{1}H $NMR_{MAJOR(SYN)}$ (600 MHz, $CDCl_3$) δ 2.68-2.78 (2H, m, C*H*$_2$), 3.07-3.14 (1H, m, C*H*$_2$), 3.24-3.30 (1H, m, C*H*$_2$), 3.41 (1H, dd, *J* = 14.8, 10.1, PhC*H*$_2$), 3.57 (1H, dd, *J* = 14.6, 3.3, PhC*H*$_2$), 4.55 (1H, d, *J* = 8.3, C*H*N), 4.89-4.94 (1H, ddd, *J* = 10.2, 8.4, 3.0, C*H*NO_2), 7.16 (2H, d, *J* = 8.5, Ar*H*), 7.23-7.25 (2H, m, Ar*H*), 7.27-7.35 (3H, m, Ar*H*), 7.62 (1H, s, Ar*H*), 7.75 (1H, br. s, N*H*); ^{1}H $NMR_{MINOR(ANTI)}$ (600 MHz, $CDCl_3$) δ 2.89-2.95 (1H, m, C*H*$_2$), 3.90 - 3.99 (1H, m, C*H*$_2$), 4.64 (1H, d, *J* = 4.9, C*H*N), 4.98-5.03 (1H, m, C*H*NO_2) other signals could not be determined.

1-(6-Bromo-1-(1-nitro-2-phenylethyl)-3,4-dihydro-1*H*-pyrido[3,4-b]indol-2(9*H*)-yl)-2,2,2-trifluoroethanone 309



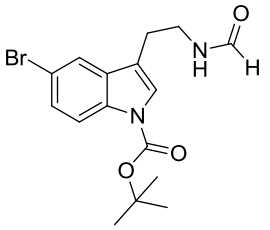
Crude *β*-nitroamine **303** was re-dissolved in CH_2Cl_2 (5 mL), cooled to 0 ^oC and then trifluoroacetic anhydride (140 μL, 1.00 mmol), followed by pyridine (80 μL, 1.00 mmol) were added at rt and the solution was stirred at rt for 2 h. After this time, 2.0 M HCl (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ 10 mL) and sat. brine (10 mL). The organic phase was then dried ($MgSO_4$) and the solvents were removed *in vacuo* to afford crude *β*-nitrotrifluoroacetamide which was purified by column chromatography (10-40% EtOAc/pet. ether) to give major diastereomer **309** (23 mg, 0.05 mmol, 23% yield) as a colourless oil which degraded at room temperature before full data could be obtained. ^{1}H $NMR_{MAJOR(SYN)}$ (600 MHz, $CDCl_3$) δ 2.88 (1H, dd, *J* = 15.8, 4.0, C*H*$_2$), 2.97 (1H, ddd, *J* = 16.8, 12.2, 5.9, C*H*$_2$), 3.23 (1H, dd, *J* = 14.7, 4.3, C*H*$_2$), 3.47 (1H, dd, *J* = 14.7, 10.2, C*H*$_2$), 3.52 (1H, ddd, *J* = 15.1, 11.9, 4.3, C*H*$_2$), 4.30 (1H, dd, *J* = 15.0, 5.4, C*H*$_2$), 5.08 (1H, apt. td, *J* = 9.7, 4.4, C*H*NO_2), 6.35 (1H, d, *J* = 9.6, C*H*N), 7.15 (2H, d, *J* = 7.2, Ar*H*), 7.20 (1H, d, *J* = 9.2, Ar*H*), 7.28-7.37 (4H, m, Ar*H*), 7.60 (1H, d, *J* = 1.5, Ar*H*), 7.86 (1H, br. s, N*H*); ^{1}H $NMR_{MINOR(ANTI)}$ (600 MHz, $CDCl_3$) δ 5.21 (1H, ddd, *J* = 10.7, 6.2, 4.1, C*H*NO_2), 6.28 (1H, d, *J* = 6.4, C*H*N) other signals could not be determined.

Bisindole 310



To a mixture of imine **304** (25 mg, 0.100 mmol) in CH_2Cl_2 (1 mL) was added *β*-nitrostyrene **84a** (15 mg, 0.100 mmol) to give a yellow solution. The reaction was stirred at rt for 4 h until precipitation occurred. The reaction mixture was then filtered to give **310** (22 mg, 0.034 mmol, 68% yield) as a yellow solid; mp 192-194 ^{o}C; IR υ_{max} 3379 (N-H), 1547 (N-O), 1445, 1374, 1312, 1225, 1112 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.37 (1H, td, *J* = 11.4, 3.4, C*H*$_2$), 2.55 (1H, br. d, *J* = 15.1, C*H*$_2$), 2.69-2.81 (2H, m, C*H*$_2$), 2.81-2.90 (1H, m, C*H*$_2$), 2.91-3.01 (2H, m, C*H*$_2$), 3.19 (1H, td, *J* = 12.2, 4.0, C*H*$_2$), 4.01 (1H, d, *J* = 10.0, C*H*N), 4.91 (1H, d, *J* = 10.4, C*H*N), 5.08 (1H, s, NC*H*N), 5.16 (1H, apt. t, *J* = 10.1, C*H*NO_2), 7.15 (1H, d, *J* = 8.5, Ar*H*), 7.24-7.27 (4H, m, Ar*H*), 7.28-7.32 (1H, m, Ar*H*), 7.34-7.44 (3H, m, Ar*H*), 7.62 (2H, dd, *J* = 6.6, 1.3, Ar*H*), 7.64 (1H, s, N*H*), 8.18 (1H, s, N*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.4 (*C*H_2), 21.8 (*C*H_2), 40.4 (*C*H_2), 47.9 (*C*H_2), 58.4 (*C*HN), 71.9 (*C*HN), 79.0 (N*C*HN), 90.2 (*C*HNO_2), 110.1 (*Ar*), 112.3 (*Ar*), 112.8 (*Ar*H), 112.9 (*Ar*H), 113.1 (*Ar*), 113.2 (*Ar*), 121.4 (*Ar*H), 121.4 (*Ar*H), 125.3 (*Ar*H), 125.6 (*Ar*H), 128.3 (*Ar*), 128.7 (*Ar*), 129.4 (*Ar*H), 131.3 (*Ar*), 131.4 (*Ar*), 135.0 (*Ar*), 135.1 (*Ar*), 136.7 (*Ar*); *m/z* (ESI$^-$) 648 (26, ^{81,81}M-H), 646 (45, ^{79,81}M-H), 644 (27, ^{79,79}M-H); HRMS $C_{30}H_{24}Br_2N_5O_2$ calcd. 644.0297, found 644.0315.

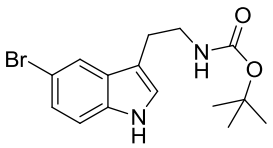
***tert*-Butyl 5-bromo-3-(2-formamidoethyl)-1H-indole-1-carboxylate 313**



Prepared using a modified literature procedure.[183] To a solution of formamide **305** (500 mg, 1.87 mmol) in THF (10 mL) was added 4-dimethylpyridine (23 mg, 0.19 mmol) and di-*tert*-butyl dicarbonate (490 mg, 2.25 mmol). The solution was heated

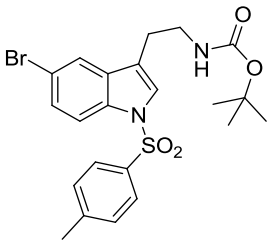
to 40 ^{o}C and stirred for 16 h. The excess solvent was then removed *in vacuo* to give crude **313** which was purified by column chromatography (2.5% MeOH/CH_2Cl_2) to give **313** (561 mg, 1.53 mmol, 82% yield) as a white solid; mp 130-133 ^{o}C; IR υ_{max} 3322 (C-H), 2980 (C-H), 1732 (C=O), 1665, 1451, 1379, 1257, 1157 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.66 (9H, s, C(*C*H$_3$)$_3$), 2.91 (2H, t, *J* = 6.9, ArC*H*$_2$), 3.63 (2H, apt. q, *J* = 6.7, C*H*$_2$NH), 5.59 (1H, br. s, N*H*), 7.42 (2H, dd, *J* = 8.8, 1.9, Ar*H*), 7.65 (1H, d, *J* = 1.7, Ar*H*), 8.02 (1H, br, Ar*H*), 8.18 (1H, s, *H*C=O); ^{1}H NMR$_{ROTAMER}$ 2.88 (2H, t, *J* = 7.0, ArC*H*$_2$), 3.56 (2H, apt. q, *J* = 6.6, C*H*$_2$NH), 7.60 (1H, d, *J* = 1.9, Ar*H*), 7.97 (1H, d, *J* = 11.9, *H*C=O); ^{13}C NMR (151 MHz, $CDCl_3$) δ 25.1 (Ar*C*H$_2$), 28.3 (C(*C*H$_3$)$_3$), 37.7 (*C*H$_2$), 84.3 (*C*Me$_3$), 116.1 (*Ar*), 116.7 (*Ar*), 117.0 (*Ar*H), 121.7 (*Ar*H), 124.6 (*Ar*H), 127.6 (*Ar*H), 132.0 (*Ar*), 134.4 (1C, br, *Ar*), 149.4 (*C*=O), 161.3 (H*C*=O); ^{13}C NMR$_{ROTAMER}$ (151 MHz, $CDCl_3$) δ 27.3 (Ar*C*H$_2$), 28.3 (C(*C*H$_3$)$_3$), 41.2 (*C*H$_2$), 84.5 (*C*Me$_3$), 115.6 (*Ar*), 116.2 (*Ar*), 117.1 (*Ar*H), 121.4 (*Ar*H), 125.0 (*Ar*H), 127.7 (*Ar*H), 131.6 (*Ar*), 149.3 (*C*=O), 164.5 (H*C*=O); *m/z* (EI) 368 (5, ^{81}M), 366 (5, ^{79}M), 267 (16, ^{81}M-Boc), 265 (17, ^{79}M–Boc); HRMS $C_{16}H_{19}BrN_2O_3$ calcd. 366.0579, found 366.0570.

tert-Butyl (2-(5-bromo-1*H*-indol-3-yl)ethyl)carbamate 316



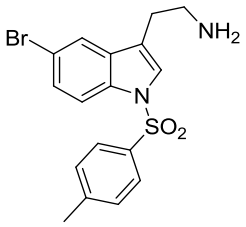
To a solution of 5-bromotryptamine (430 mg, 1.80 mmol) in Me_2CO/water (1:1, 30 mL) was added K_2CO_3 (500 mg, 3.60 mmol) and di-*tert*-butyl dicarbonate (420 mg, 1.93 mmol) and the mixture was stirred for 16 h at rt. The excess solvent was removed *in vacuo* and the resultant residue was extracted with EtOAc (40 mL), dried ($MgSO_4$) and the excess organics were removed *in vacuo* to give crude **316** (632 mg, quantitative yield) as a colourless oil which was used without further purification; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.46 (9H, s, C(*C*H$_3$)$_3$), 2.87 (2H, t, *J* = 6.8, ArC*H*$_2$), 3.41 (2H, br. q, *J* = 6.2, C*H*$_2$NH), 4.76 (1H, br. s, N*H*CO), 6.95 (1H, s, Ar*H*), 7.20 (1H, d, *J* = 8.1, Ar*H*), 7.24 (1H, dd, *J* = 8.3, 1.9, Ar*H*), 7.70 (1H, s, Ar*H*), 8.78 (1H, br. s, N*H*); ^{1}H NMR data are consistent with literature data.[184]

tert-Butyl (2-(5-bromo-1-tosyl-1*H*-indol-3-yl)ethyl)carbamate 317



Prepared using a modified literature procedure.[185] To a solution of **316** (150 mg, 0.44 mmol) in THF (5 mL) was added *para*-toluenesulfonyl chloride (95 mg, 0.50 mmol) and potassium *tert*-butoxide (100 mg, 0.88 mmol) and the suspension was stirred for 16 h at rt. Water (5 mL) was then added and the excess organics were removed *in vacuo*. Sat. aq. $NaHCO_3$ 5 mL) was added and the reaction was extracted with EtOAc (2 x 10 mL), dried ($MgSO_4$) and the excess solvent removed to give **317** (223 mg, 0.45 mmol, quantitative yield) as a yellow oil; IR υ_{max} 3354 (N-H), 2977 (C-H), 2930 (C-H), 1702, 1512, 1442, 1366, 1169 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.45 (9H, s, C(*C*H$_3$)$_3$), 2.34 (3H, s, ArC*H*$_3$), 2.81 (2H, t, *J* = 6.6, ArC*H*$_2$), 3.38 (2H, apt. q, *J* = 6.1, C*H*$_2$NH), 4.58 (1H, br. s, N*H*), 7.19-7.24 (2H, m, Ar*H*), 7.37 (1H, s, Ar*H*), 7.40 (1H, dd, *J* = 8.8, 1.8, Ar*H*), 7.60 (1H, d, *J* = 1.7, Ar*H*), 7.71 (2H, d, *J* = 8.5, Ar*H*), 7.84 (1H, d, *J* = 8.8, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.7 (Ar*C*H$_3$), 25.6 (*C*H$_2$), 28.5 (C(*C*H$_3$)), 40.2 (*C*H$_2$), 79.7 (*C*Me$_3$), 115.3 (*Ar*H), 116.9 (*Ar*), 119.6 (*Ar*), 122.4 (*Ar*H), 124.8 (*Ar*H), 126.9 (*Ar*H), 127.8 (*Ar*H), 130.1 (*Ar*H), 132.7 (*Ar*), 134.1 (*Ar*), 134.9 (*Ar*), 145.3 (*Ar*), 155.9 (*C*=O); *m/z* (EI) 494 (3, ^{81}M), 492 (3, ^{79}M), 377 (13, ^{81}M–NH_2Boc), 375 (13, ^{79}M–NH_2Boc); HRMS $C_{22}H_{25}BrN_2O_4S$ calcd. 492.0718, found 492.0727.

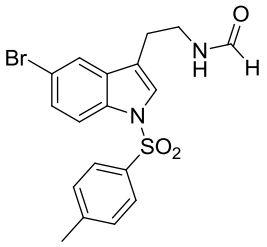
2-(5-Bromo-1-tosyl-1*H*-indol-3-yl)ethanamine 318



Pre-cooled (ice bath, 0 ^{o}C) TFA (10 mL) was added to a cooled flask (ice bath, 0 ^{o}C) containing **317** (195 mg, 0.365 mmol). The resultant yellow solution which was stirred at 0 ^{o}C for 2 h to give a red solution. The excess solvent was then removed *in vacuo* and the concentrated residue was cooled to 0 ^{o}C. To this was added 2.0 M

NaOH (20 mL) and 5% MeOH/CH_2Cl_2 (30 mL) and the mixture was stirred for 15 min. The biphasic mixture was then separated and the aqueous phase was re-extracted with more CH_2Cl_2 (2 x 10 mL). The combined organics were dried (Na_2SO_4) and excess solvent removed to give **318** (146 mg, 0.372 mmol, 94% yield) as a yellow oil; IR υ_{max} 2924 (C-H), 1711, 1442, 1370, 1171 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.35 (3H, s, C*H*$_3$), 2.76 (2H, t, *J* = 6.6, ArC*H*$_2$), 2.99 (2H, t, *J* = 6.8, C*H*$_2$), 7.22 (2H, d, *J* = 7.9, Ar*H*), 7.38 (1H, s, Ar*H*), 7.41 (1H, dd, *J* = 8.7, 1.9, Ar*H*), 7.62 (1H, d, *J* = 1.7, Ar*H*), 7.73 (2H, d, *J* = 8.5, Ar*H*), 7.86 (1H, d, *J* = 8.8, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.7 (*C*H$_3$), 29.2 (*C*H$_2$), 41.5 (*C*H$_2$), 115.4 (*Ar*H), 116.8 (*Ar*), 120.1 (*Ar*), 122.4 (*Ar*H), 124.7 (*Ar*H), 126.8 (*Ar*H), 127.7 (*Ar*H), 130.1 (*Ar*H), 132.8 (*Ar*), 134.2 (*Ar*), 135.0 (*Ar*), 145.3 (*Ar*); *m/z* (EI) 394 (14, ^{81}M), 392 (14, ^{79}M), 365 (34, $^{81}M–NH_2CH_2$), 363 (32, $^{79}M–NH_2CH_2$); HRMS $C_{17}H_{17}BrN_2O_2S$ calcd. 392.0194, found 392.0182.

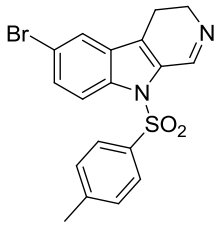
_N_-(2-(5-Bromo-1-tosyl-1_H_-indol-3-yl)ethyl)formamide 319



A mixture of tryptamine **318** (1.25 g, 3.18 mmol) in ethylformate (50 mL) was heated at reflux (56 ^oC) for 2 h, or until reaction complete as judged by tlc analysis, and then cooled to rt. The excess solvent was then removed *in vacuo* to give crude **319** (1.39 g, quantitative yield) as an off-white solid; mp 119-121 ^oC; IR υ_{max} 3256, 3044, 2871 (C-H), 1740, 1651 (C=O), 1442, 1372, 1293, 1164 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 2.35 (3H, s, C*H*$_3$), 2.87 (1H, t, *J* = 6.9, ArC*H*$_2$), 3.59 (1H, apt. q, *J* = 6.7, C*H*$_2$NH), 5.57 (1H, br. s, N*H*), 7.24 (2H, d, *J* = 7.9, Ar*H*), 7.39-7.44 (2H, m, Ar*H*), 7.62 (1H, d, *J* = 1.9, Ar*H*), 7.71-7.74 (2H, m, Ar*H*), 7.86 (1H, d, *J* = 8.7, Ar*H*), 8.17 (1H, s, *H*C=O); ^1H NMR$_{ROTAMER}$ (600 MHz, $CDCl_3$) δ 2.85 (2H, t, *J* = 6.6, ArC*H*$_2$), 3.50 (2H, apt. q, *J* = 6.7, C*H*$_2$NH), 7.57 (1H, d, *J* = 1.7, Ar*H*), 7.88-7.92 (1H, m, Ar*H*) remaining signals could not be determined; ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.7 (*C*H$_3$), 25.1 (*C*H$_2$), 37.6 (*C*H$_2$), 115.4 (*Ar*H), 117.0 (*Ar*), 118.9 (*Ar*), 122.3 (*Ar*H), 124.8 (*Ar*H), 126.9 (*Ar*H), 128.0 (*Ar*H), 130.1 (*Ar*H), 132.4 (*Ar*), 134.1 (*Ar*), 134.9 (*Ar*), 145.5 (*Ar*), 161.3 (O=*C*H); ^{13}C NMR$_{ROTAMER}$ (151 MHz, $CDCl_3$) δ 27.3 (*C*H$_2$),

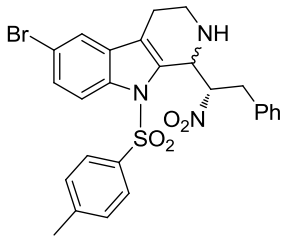
41.0 (*C*CH_2), 115.6 (*Ar*H), 122.0 (*Ar*H), 125.3 (*Ar*H), 128.1 (*Ar*H), 130.2 (*Ar*H), 132.0 (*Ar*), 145.6 (*Ar*), 164.3 (O=C*H*) remaining signals could not be determined; *m/z* (EI) 422 (5, ^{81}M), 420 (5, ^{79}M), 377 (57, ^{81}M–$NCOH_3$), 375 (55, ^{79}M-$NCOH_3$); HRMS $C_{18}H_{17}BrN_2O_3S$ calcd. 420.0143, found 420.0134.

6-Bromo-9-tosyl-4,9-dihydro-3*H*-pyrido[3,4-b]indole 315



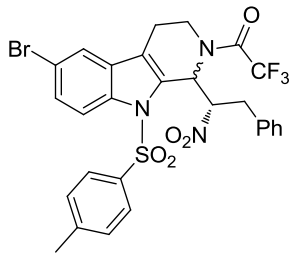
To a flame-dried schlenk flask was added formamide **319** (40 mg, 0.095 mmol) and the flask was placed under vacuum and evacuated/backfilled with nitrogen three times. To this was then added acetonitrile (degassed freeze/pump/thaw three times, 2 mL). To this solution $POCl_3$ (90 μL, 0.950 mmol) was added dropwise over 5 min. After complete addition the reaction was submerged in an oil bath pre-heated to 85 ^{o}C. The reaction was stirred for 16 h at reflux and then allowed to cool to rt. The excess solvent was removed and the residue was partitioned in EtOAc (20 mL) and 2 M NaOH (10 mL). The bi-phasic mixture was separated and the organic was dried (Na_2SO_4) and the excess solvent removed to give crude **315** which was purified by column chromatography (80% EtOAc/pet. ether) to give **315** (17 mg, 0.042 mmol, 44% yield) as a yellow oil; IR υ_{max} 2924 (C-H), 1726, 1596, 1549, 1438, 1380, 1358, 1172 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.35 (3H, s, CH_3), 2.73 (2H, apt. t, *J* = 8.8, ArCH_2), 3.86 (2H, apt. td, *J* = 8.8, 2.1, CH_2N), 7.21 (2H, d, *J* = 8.3, Ar*H*), 7.53 (1H, dd, *J* = 8.9, 1.8, Ar*H*), 7.61 (1H, d, *J* = 1.7, Ar*H*), 7.65 (2H, d, *J* = 8.5, Ar*H*), 8.07 (1H, d, *J* = 8.8, Ar*H*), 8.99 (1H, s, N=C*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 18.7 (*C*CH_2), 21.7 (*C*CH_3), 47.3 (*C*CH_2), 116.7 (*Ar*H), 117.8 (*Ar*), 123.1 (*Ar*H), 124.6 (*Ar*), 126.7 (*Ar*H), 129.6 (*Ar*), 129.7 (*Ar*), 130.1 (*Ar*H), 130.3 (*Ar*H), 134.6 (*Ar*), 135.6 (*Ar*), 145.6 (*Ar*), 150.9 (N=*C*H); *m/z* (ESI^{+}) 405 (98, ^{81}M+H), 403 (100, ^{79}M+H), 250 (38, ^{81}M+H-Ts), 248 (40, ^{79}M+H-Ts); HRMS $C_{18}H_{15}BrN_2O_2SH^{+}$ calcd. 403.0116, found 403.0110.

6-Bromo-1-((S)-1-nitro-2-phenylethyl)-9-tosyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indole 320



To a flask containing imine **315** (17 mg, 0.042 mmol) in toluene (0.5 mL) was added *β*-nitrostyrene **84a** (12 mg, 0.080 mmol) and Hantzsch ester **254** (25 mg, 0.080 mmol) and the mixture was cooled to -20 ^{o}C. A solution of catalyst **272** (45 μL, 0.008 mmol, 0.184 M in toluene) was then added and the reaction was stirred at room temperature for 24 h. After this time, a small aliquot (10 μL) was removed and analysed by ^{1} H NMR to measure reaction progress; ^{1}H NMR_{MAJOR} (400 MHz, $CDCl_3$) δ 2.34 (3H, s, ArC*H*$_3$), 3.47 (1H, dd, *J* = 14.6, 9.5, PhC*H*$_2$), 5.31-5.37 (1H, m, C*H*N), 5.92 (1H, ddd, *J* = 9.5, 4.0, 3.0, C*H*NO_2) remaining signals could not be determined; ^{1}H NMR_{MINOR} (400 MHz, $CDCl_3$) δ 3.75 (1H, dd, *J* = 14.3, 10.5, PhC*H*$_2$), 5.60 (1H, apt. dt, *J* = 10.5, 4.8, C*H*NO_2) remaining signals could not be determined.

1-(6-Bromo-1-((S)-1-nitro-2-phenylethyl)-9-tosyl-3,4-dihydro-1*H*-pyrido[3,4-b]indol-2(9H)-yl)-2,2,2-trifluoroethanone 321



To the reaction flask containing crude **320** was added trifluoroacetic anhydride (28 μL, 0.200 mmol), followed by $^{i}Pr_2NEt$ (33 μL, 0.200 mmol) were added and the solution was stirred at rt for 1 h. After this time, 2.0 M HCl (2 mL) was added and the aqueous phase was extracted with Et_2O (2 x 5 mL) and the combined organic phases were washed with sat. aq. $NaHCO_3$ 5 mL) and sat. brine (5 mL). The organic phase was then dried ($MgSO_4$) and the solvents were removed *in vacuo* to afford crude *β*-nitrotrifluoroacetamide **321** which was purified by chromatography (20% Me_2CO/pet. ether then 20% EtOAc/pet. ether) to give major diastereomer **321** (9 mg,

0.014 mmol, 33% yield) as a colourless oil; HPLC analysis (Chiralcel AD, hexane/*iso*-propanol 90:10, flow rate = 1 mL/min, λ = 254 nm): retention time t_r (major) = 18.7 min, t_r (minor) = 32.5 min, shows 48% *ee*; IR υ_{max} 2924 (C-H), 1697 (C=O), 1557 (N-O), 1441, 1368 (N-O), 1207, 1170 cm^{-1}; ^1H NMR_{MAJOR} (600 MHz, $CDCl_3$) δ 2.32 (3H, s, ArC*H*$_3$), 2.77-2.89 (2H, m, C*H*$_2$), 2.91 (1H, dd, *J* = 14.7, 2.4, PhC*H*$_2$), 3.55 (1H, dd, *J* = 14.5, 11.9, PhC*H*$_2$), 3.88 (1H, ddd, *J* = 15.6, 11.3, 4.9, C*H*$_2$N), 4.31 (1H, apt. dd, *J* = 14.8, 6.1, C*H*$_2$N), 5.86 (1H, ddd, *J* = 11.9, 5.3, 2.6, C*H*NO_2), 7.07 (1H, d, *J* = 5.3, C*H*N), 7.12 (2H, d, *J* = 7.2, Ar*H*), 7.18-2.28 (4H, m, Ar*H*), 7.49 (1H, d, *J* = 1.9, Ar*H*), 7.51-7.55 (2H, m, Ar*H*), 7.61-7.65 (2H, m, Ar*H*), 8.13 (1H, d, *J* = 8.8, Ar*H*); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.5 (*C*H_2), 21.8 (Ar*C*H_3), 35.9 (Ph*C*H_2), 40.5 (*C*H_2N), 52.0 (*C*HN), 90.7 (*C*HNO_2), 116.3 (1C, q, *J* = 287.8, *C*F_3), 117.7 (*Ar*H), 118.6 (*Ar*), 120.7 (*Ar*), 122.0 (*Ar*H), 127.0 (*Ar*H), 127.6 (*Ar*H), 128.8 (*Ar*H), 129.1 (*Ar*H), 129.4 (*Ar*H), 129.5 (*Ar*), 130.3 (*Ar*H), 131.0 (*Ar*), 133.1 (*Ar*), 135.5 (*Ar*), 136.2 (*Ar*), 146.2 (*Ar*), 157.5 (1C, q, *J* = 287.8, *C*=O); *m/z* (EI) 651 (7, ^{81}M), 649 (7, ^{79}M), 605 (8, ^{81}M-NO_2), 603 (8, ^{79}M-NO_2), 501 (92, ^{81}M-NO_2CHCH_2Ph), 499 (88, ^{79}M-NO_2CHCH_2Ph); HRMS $C_{28}H_{23}BrF_3N_3O_5S$ calcd. 649.0494, found 649.0519.

Chapter 5. Appendices

5.1 Abbreviations

δ	chemical shift
Å	Angstrom
Ac	acetyl
AIBN	azobis*iso*butyronitrile
anal.	analysis
aq.	aqueous
Ar	aryl
atm	atmosphere
BAM	bisamidine
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyl carbonyl
BOX	3-[(*E*)-2-butenoyl]-1,3-oxazolidin-2-one
bp	boiling point
Bt	benzotriazyl
^{i}Bu	*iso*-butyl
^{n}Bu	*n*-butyl
^{t}Bu	*tert*-butyl
C	celcius
ca.	approximately
calcd.	calculated
CAN	ceric ammonium nitrate
Cat	catalyst
Cbz	carboxybenzyl
CDC	cross-dehydrogenative coupling
CI	chemical ionisation
conv.	conversion
CPME	cyclopentylmethyl ether

Cy	cyclohexyl
d	day
DBU	1,8-diazabicycloundec-7-ene
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DCM	CH2Cl2
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DIPEA	di*iso*propylethylamine
DMAP	*N*,*N*-4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
E^+	electrophile
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
EI	electron impact
ESI	electrospray ionisation
Et	ethyl
equiv.	equivalents of
FAB	fast atom bombardment
Fu	furyl
g	gram
h	hour
HBA	hydrogen bond acceptor
H-bond	hydrogen bond
HBTU	*N*,*N*,*N'*,*N'*-tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
Hex	hexyl
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HIV	human immunodeficiency virus
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry

Hz	hertz
IR	infrared spectroscopy
J	coupling constant
J	joule
kcal	kilocalorie
LA	Lewis acid
Lit.	literature
LUMO	lowest unoccupied molecular orbital
m	*meta*
M	mole per litre
MBH	Morita-Bayliss-Hilman
*m*CPBA	*meta*- chloroperoxybenzoic acid
Me	methyl
mg	milligram
MHz	megahertz
min	minute
mL	millilitre
mmol	millimole
mol%	mole percentage
mp	melting point
MS	molecular sieves
Ms	mesyl chloride
Naph	naphthyl
NIS	*N*-iodosuccinimide
NME	(-)-*N*-methylephedrine
NMR	nuclear magnetic resonance
Nu	nucleophile
o	*ortho*
OMB	*ortho*-methoxybenzyl
p	*para*
pet.	petroleum
PG	protecting group
Ph	phenyl

PMB	*para*-methoxybenzyl
PMHS	polymethylhydrosiloxane
PMP	*para*-methoxyphenyl
^{n}Pn	*n*-pentyl
ppm	parts per million
^{i}Pr	*iso*-propyl
^{n}Pr	*n*-propyl
p-TSA	*para*-toluenesulfonic acid monohydrate
Py	pyridyl
Pyr	pyrrole
Ra-Ni	Raney® Nickel
Rf	retention factor
rt	room temperature
rxn.	reaction
sat.	saturated
Temp.	temperature
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium triphenylsilyl difluorosilicate
TBDMS	*t*ert-butyldimethylsilyl
TBHP	*tert*-butylhydroperoxide
TBME	*tert*-butylmethyl ether
TEA	triethylamine
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
tlc	thin layer chromatography
TMS	trimethylsilyl
Tol	*para*-tolyl
TOF	time of flight
Ts	*para*-toluenesulfonyl
TS	transition state
uv	ultraviolet

5.2 Table of coupling constants for *β*-nitroamines

As depicted in figure 34, it is thought that the *β*-nitroamines exist in a *pseudo* chair conformation allowing the assignment of the relative stereochemistry based on the coupling constant between the protons in the *α*-position of the amino and nitro groups.

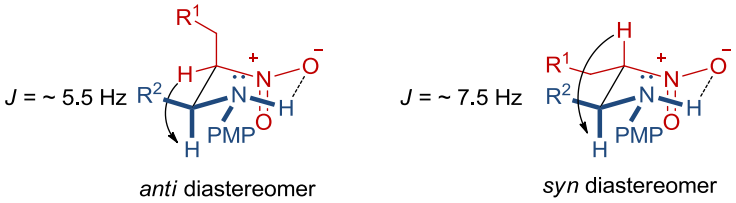
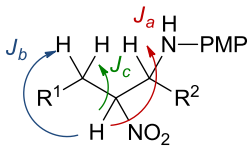
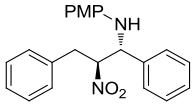
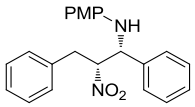
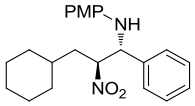
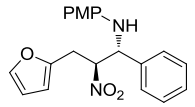
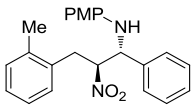
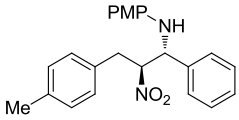
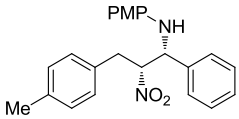
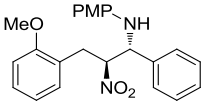
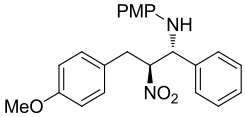
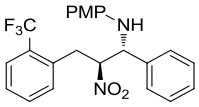
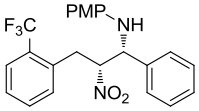
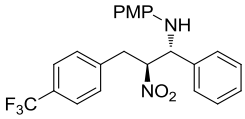
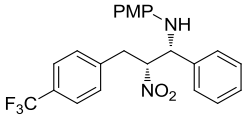


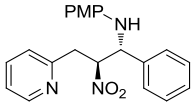
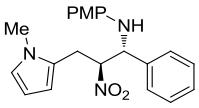
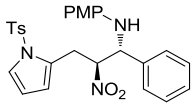
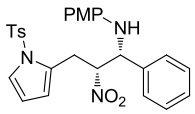
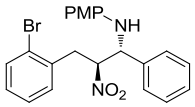
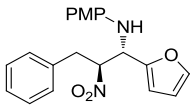
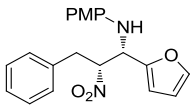
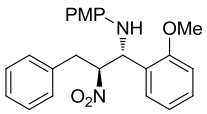
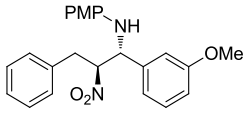
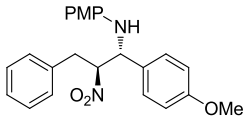
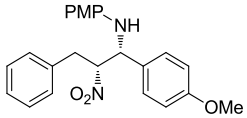
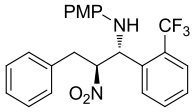
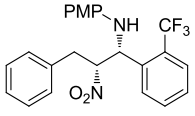
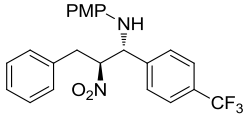
Figure 34. Assignment of relative stereochemistry

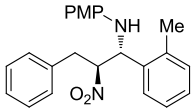
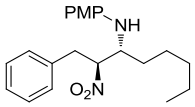
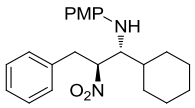
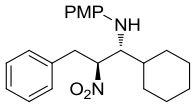
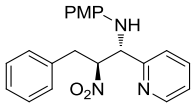
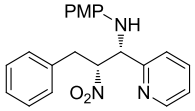
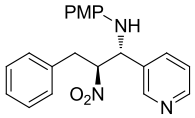
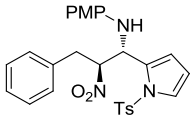
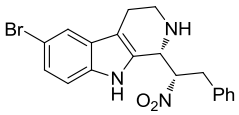
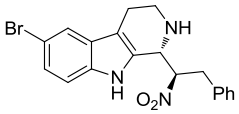
The following table lists the structure and the ^{1}H NMR coupling constants of several *β*-nitroamines synthesised. The relative diastereochemistry was then assigned based on the J_a-value. Typically, the *anti* diasteromer had a coupling constant of approximately 5.5 Hz whereas the J_a-value for the *syn* diastereomer was greater than 7.0 Hz. Coupling constants were taken as an average of the two *J*-values except where only one was visible in the crude ^{1}H NMR spectra. For some *β*-nitroamines the J_a-value could not be determined due to overlapping signals and hence these are not in the table. However these *β*-nitroamines have been tentatively assigned as *anti* diasteromers based on the results from other analogues.

Table 20. Coupling constants for *β*-nitroamines for assignment of relative stereochemistry



Entry	*β*-Nitroamine		J_a [a]	J_b [a]	J_c [a]
1		**237aa major**	5.4	10.5	3.6
2		**237aa minor**	7.2	9.4	5.3
3		**237ba major**	5.5	11.2	2.6
4		**237da major**	5.5	9.9	4.3
5		**237ea major**	5.5	10.8	3.0
6		**237fa major**	5.6	10.3	3.6
7		**237fa minor**	7.3	9.6	5.3
8		**237ga major**	5.3	9.8	3.5
9		**237ha major**	5.7	10.4	3.6
10		**237ia major**	6.8	11.4	2.3
11		**237ia minor**	8.3	10.9	2.6
12		**237ja major**	5.8	10.8	3.3
13		**237ja minor**	7.6	10.0	5.0

14		**237ka major**	5.8	9.5	4.0
15		**237ma major**	5.3	9.3	4.0
16		**237na major**	7.6	10.7	2.2
17		**237na minor**	8.7	11.2	3.6
18		**237oa major**	5.9	10.9	2.9
19		**237ab major**	5.7	5.3	9.0
20		**237ab minor**	7.5	5.2	9.6
21		**237ac major**	7.5	11.5	4.0
22		**237ad major**	5.5	10.6	3.8
23		**237ae major**	5.8	9.5	3.7
24		**237ae minor**	7.5	9.8	4.8
25		**237af major**	4.8	11.8	2.8
26		**237af minor**	4.3	8.5	6.6
27		**237ag major**	5.6	10.5	3.7

28		**237ah major**	6.0	11.5	2.6
29		**237ai major**	4.2	8.4	6.4
30		**237aj major**	7.8	9.4	4.9
31		**237aj minor**	4.9	9.1	5.5
32		**237ak major**	7.3	10.0	4.0
33		**237ak minor**	6.3	9.8	5.0
34		**237al major**	5.5	10.0	4.3
35		**237ao major**	5.8	10.7	2.8
36		**303 major**	8.4	10.2	3.0
37		**303 minor**	4.9	n.d	n.d

[a] *J*-values are given as an average of two values unless only one could be determined.

5.3 References

[1] Palomo, C.; Oiarbide, M.; Garcia, J.M. *Chem. Soc. Rev.* **2004**, *33*, 65.

[2] Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, *16*, 2561.

[3] Shibasaki, M.; Matsunaga, S. *J. Organomet. Chem*. **2006**, *691*, 2089.

[4] Henry, L. *Bull. Acad. Roy. Belg.* **1896**, *32*, 33.

[5] Adams, H.; Anderson, J. C.; Peace, S.; Pennel, A. M. K. *J. Org. Chem.* **1998**, *63*, 9932.

[6] (a) Westermann, B. *Angew. Chem. Int. Ed.* **2003**, *42*, 151. (b) Marquéz-López, E.; Merino, P.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2009**, 2401.

[7] Mousset, T. *Bull. Acad. Roy. Belg.* **1901**, 622.

[8] (a) Senkus, M. *J. Am. Chem. Soc.* **1946**, *68*, 10. (b) Johnson, H. G. *J. Am. Chem. Soc.* **1946**, *68*, 12.

[9] Hurd, C. D.; Strong, J. S. *J. Am. Chem. Soc.* **1950**, *72*, 4813.

[10] (a) Duden, P.; Bock, K.; Reid, H. J. *Chem. Ber.* **1905**, 2036. (b) Cerf de Mauny, H. *Compt. Rend.* **1932**, 1084. (c) Jones, J. K. N.; Urbanski, T. *J. Am. Chem. Soc.* **1949**, *71*, 1766. (d) Grillot, G. F.; Bashford, R. I. *J. Am. Chem. Soc.* **1951**, *73*, 5598. (e) Butler, G. B. *J. Am. Chem. Soc.* **1956**, *78*, 482. (f) Smiley, R. A. *J. Org. Chem.* **1958**, *23*, 1115. (g) Bhagwatheeswara, H.; Gaur, S. P.; Jain, C. *Synthesis* **1976**, 615.

[11] Ballini, R.; Petrini, M. *Tetrahedron Lett.* **1999**, *40*, 4449.

[12] Anderson, J. C.; Peace, S.; Pih, S. *Synlett* **2000**, *6*, 850.

[13] (a) Ruano, J. L. G.; López-Cantarero, J.; Haro, T. D.; Alemán, J.; Cid, M. B. *Tetrahedron* **2006**, *62*, 12197. (b) Kattuboina, K.; Kaur, P.; Ai, T.; Li, G. *Chem. Biol. Drug Des.* **2008**, *71*, 216. (c) Pindi, S.; Kaur, P.; Shakya, G.; Li, G. *Chem. Biol. Drug Des.* **2011**, *77*, 20.

[14] Ruano, J. L. G.; Topp, M.; López- Cantarero, J.; Alemán, J.; Remuinán, M. J.; Cid, M. B. *Org. Lett.* **2005**, *7*, 4407.

[15] Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 3504.

[16] Yamada, K.; Moll, G.; Shibasaki, M. *Synlett* **2001**, *7*, 980.

[17] Anderson, J. C.; Blake, A. J.; Howell, G. P.; Wilson, C. *J. Org. Chem.* **2005**, *70*, 549.

[18] Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843.

[19] Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem.. Int. Ed.* **2001**, *40*, 2992.

[20] Lee, A.; Kim, W.; Lee, J.; Hyeon, T.; Kim, B. M. *Tetrahedron: Asymmetry* **2004**, *15*, 2595.

[21] Anderson, J. C.; Howell, G. P.; Lawrence, R. M.; Wilson, C. S. *J. Org. Chem.* **2005**, *70*, 5665.

[22] Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; López, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 117.

[23] (a) Gao, F.; Zhu, J.; Tang, Y.; Deng, M.; Qian, C. *Chirality*, **2006**, *18*, 741. (b) Trost, B. M.; Lupton, D. W.; *Org. Lett.* **2007**, *9*, 2023.

[24] Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900.

[25] Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 4925.

[26] Tan, C.; Liu, X.; Wang, L.; Wang, J.; Feng, X. *Org. Lett.* **2008**, *10*, 5305.

[27] Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.; Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496.

[28] (a) Tu, Y.; Wang, Z.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Denmark, S. E.; Wu, Z.; Crudden, C.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288. (c) Yang, D.; Yip, Y.; Tang, M.; Wong, M.; Zheng, J.; Cheung, K. *J. Am. Chem. Soc.*, **1996**, *118*, 491. (d) Sigman, M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (e) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157. (f) List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (g) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

[29] Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625.

[30] Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2006**, *12*, 466.

[31] Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418.

[32] Davis, T. A.; Wilt, J. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2010**, *132*, 2880.

[33] Yoon, T. P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 466.

[34] (a) Palomo, C.; Oiarbide, M.; Laso, A.; López, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622. (b) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7975.

[35] Gomez-Bengoa, E.; Linden, A.; López, R.; Múgica-Mendiola, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955.

[36] Wang, C.; Dong, X.; Zhang, Z.; Xue, Z.; Teng, H. *J. Am. Chem. Soc.* **2008**, *130*, 8606.

[37] Xie, H.; Zhang, Y.; Zhang, S.; Chen, X.; Wang, W. *Angew. Chem. Int. Ed.* **2011**, *50*, 11773.

[38] Li, Z.; Li, C. *J. Am. Chem. Soc.* **2005**, *127*, 3762.

[39] Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Nat. Acad. Sci.* **2006**, *103*, 8928.

[40] Baslé, O.; Li, C.-J. *Green Chem.* **2007**, *9*, 1047.

[41] Boess, E.; Schmitz, C.; Klussmann, M. *J. Am. Chem. Soc.* **2012**, *134*, 5317.

[42] Tsang, A. S.-K.; Todd, M. H. *Tetrahedron Lett.* **2009**, *50*, 1199.

[43] Shu, X.-Z.; Xia, X.-F.; Yang, Y.-F.; Ji, K.-G.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2009**, *74*, 7464.

[44] Condie, A. G.; González-Gómez, J. C.; Stephenson, R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464.

[45] Yadav, J. S.; Reddy, B. V. S.; Yadav, N. N.; Gupta, M. K. *Synthesis* **2009**, 1131.

[46] Walser, A.; Benjamin, L. E.; Flynn, T.; Mason, C.; Schwartz, R.; Fryer, R. I. *J. Org. Chem.* **1978**, *43*, 936.

[47] Padwa, A.; Chen, Y.-Y.; Chiacchio, U.; Dent, W. *Tetrahedron* **1985**, *41*, 3529.

[48] (a) Ayerbe, M.; Arrieta, A.; Cossío, F. P. *J. Org. Chem.* **1998**, *63*, 1795. (b) Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F. P. *J. Am. Chem. Soc.* **2000**, *122*, 6078. (c) Zubia, A.; Mendoza, L.; Vivanco, S.; Aldaba, E.; Carrascal, T.; Lecea, B.; Arrieta, A.; Zimmerman, T.; Vidal-Vanaclocha, F.; Cossío, F. P. *Angew. Chem. Int. Ed.* **2005**, *44*, 2903. (d) Arrieta, A.; Otaegui, D.; Zubia, A.; Cossío, F. P.; Díaz-Ortiz, A.; de la Hoz, A.; Herrero, M. A.; Prieto, P.; Foces-Foces, C.; Pizarro, J. L.; Arriortua, M. I. *J. Org. Chem.* **2007**, *72*, 4313.

[49] (a) Cabrera, S.; Arrayás, R. G.; Carratero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. (b) Cabrera, S.; Arrayás, R. G.; Martín-Matute, B.; Cossío, F. P.; Carratero, J. C. *Tetrahedron* **2007**, *63*, 6587. (c) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem. Int. Ed.* **2006**, *45*, 1979. (c) Arai, T.; Mishiro, A.; Yokoyama, N.; Suzuki, K.; Sato, H. *J. Am. Chem. Soc.* **2010**, *132*, 5338. (d) Arai, T.; Yokoyama, N.; Mishiro, A.; Sato, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 7895. (e) Kim, H. Y.; Li, J.-Y.; Kim, S.; Oh, K. *J. Am. Chem. Soc.* **2011**, *133*, 20750. (f) Xue, M.-X.; Zhang, X.-M.; Gong, L.-Z. *Synlett* **2008**, 691. (g) Liu, Y.-K.; Liu, H.; Du, W.; Yue, L.; Chen, Y.-C. *Chem. Eur. J.* **2008**, *14*, 9873. (h) Xie, J.; Yoshida, K.; Takasu, K.; Takemoto, Y. *Tetrahedron Lett.* **2008**, *49*, 6910.

[50] Wang, X.; Chen, Y.; Niu, L.; Xu, P. *Org. Lett.* **2009**, *11*, 3310.

[51] Wang Y; Yu, D.-F.; Liu, Y.-Z.; Wei, H.; Luo, Y.-C.; Dixon, D. J.; Xu, P.-F. *Chem. Eur. J.* **2010**, *16*, 3922.

[52] (a) Urushima, T.; Sakamoto, D.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2010**, *12*, 4588. (b) Imashiro, R.; Uehara, H.; Barbas III, C. F. *Org. Lett.* **2010**, *12*, 5250. (c) Rai, A.; Singh, A. K.; Singh, S.; Yadav, L. D. S. *Synlett* **2011**, 335. (d) Rai, A.; Singh, A. K.; Singh, P.; Yadav, L. D. S. *Tetrahedron Lett.* **2011**, *52*, 1354.

[53] Anderson, J. C.; Stepney, G. J.; Mills, M. R.; Horsfall, L. R.; Blake, A. J.; Lewis, W. *J. Org. Chem.* **2011**, *76*, 1961.

[54] (a) Mampreian, D. M.; Hoveyda, A. H. *Org. Lett.* **2004**, *6*, 2829. (b) Côté, A.; Lindsay, V. N.; Charette, A. B. *Org. Lett.* **2007**, *9*, 85.

[55] Anderson, J. C., Horsfall, L. R., Kalogirou, A. S., Mills, M. R., Stepney, G. J., Tizzard, G. J. *J. Org. Chem.* **2012**, *77*, 6186.

[56] Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580.

[57] Ono, N. *The Nitro Group in Organic Synthesis*, John Wiley and Sons, New York, **2001**.

[58] Sturgess, M. A.; Yarberry, D. J. *Tetrahedron Lett.* **1993**, 4743.

[59] Tsuritani, N.; Yamada, K.; Yoshikawa, N.; Shibasaki, M. *Chem. Lett.* **2002**, 276.

[60] Davis, T. A.; Johnston, J. N. *Chem. Sci.* **2011**, *2*, 1076.

[61] Anderson, J. C.; Chapman, H. A. *Synthesis* **2006**, 3309.

[62] Nef, J. U. *Liebigs Ann. Chem.* **1894**, 280.

[63] Sabelle, S.; Lucet, D.; Le Gall, T.; Mioskowski, C. *Tetrahedron Lett.* **1998**, *39*, 2111.

[64] (a) Kumaraswamy, G.; Pitchaiah, A. *Helv. Chim. Acta* **2011**, *94*, 1543. (b) Liu, X.; Yan, Y.; Wang, Y.; Wang, C.; Sun, J. *Chem. Eur. J.* **2012**, *18*, 9204.

[65] Foresti, E.; Palmieri, G.; Petrini, M.; Profeta, R. *Org. Biomol. Chem.* **2003**, *1*, 4275.

[66] Blay, G.; Escamilla, A.; Hernandez-Olmos, V.; Pedro, J. R.; Sanz-Marco, A. *Chirality* **2012**, *24*, 441.

[67] Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110.

[68] Shen, B.; Makley, D. M.; Johnston, J. N. *Nature* **2010**, *465*, 1027.

[69] (a) Yoshikawa, M.; Cha, B. C.; Okaichi, Y.; Takinami, Y.; Yokokawa, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1988**, *36*, 4236. (b) Crossley, M. J.; King, L. G. *J. Org. Chem.* **1993**, *58*, 4370. (c) Voituriez, A.; Moulinas, J.; Kouklovsky, C.; Langlois, Y. *Synthesis* **2003**, 1419. (d) Kamimura, A.; Nagata, Y.; Kadowaki, A.; Uchida, K.; Uno, H. *Tetrahedron* **2007**, *63*, 11856.

[70] (a) Hynes, P. S.; Stupple, P. A.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 1389. (b) Shen, B.; Johnston, J. N. *Org. Lett.* **2008**, *10*, 4397. (c) Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632. (d) Kyle, A. F.; Jakubec, P.; Cockfield, D. M.; Cleator, E.; Skidmore, J.; Dixon, D. J. *Chem. Comm.* **2011**, *47*, 10037. (e) Jakubec, P.; Kyle, A. F.; Calleja, J.; Dixon, D. J. *Tetrahedron Lett.* **2011**, *52*, 6094. (f) Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88.

[71] (a) Yamamoto, H. *Lewis Acids in Organic Synthesis*, Wiley-VCH, Weinheim, **2000**. (b) Yamamoto, H. *Lewis Acid Reagents*, Oxford University Press, New York, **1999**. (c) Ojima, I. *Catalytic Asymmetric Synthesis* 2nd Ed., Wiley-VCH, Weinheim, **2000**. (d) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*, Springer, New York, **1999**. (e) Noyori, R. *Asymmetric Catalysis In Organic Synthesis*, Wiley-VCH, Weinheim, **1994**.

[72] (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, 999. (b) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, 395.

[73] (a) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418. (b) Gaunt, M. J.; Johnasson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8. (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (d) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638. (e) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187. (f) Pihko, P. M. *Hydrogen Bonding In Organic Synthesis*, Wiley-VCH, Weinheim, **2009**, 141-351.

[74] Hine, J.; Ahn, K.; Gallucci, J. C.; Linden, S.-M. *J. Am. Chem. Soc.* **1984**, *106*, 7980.

[75] (a) Hine, J.; Ahn, K. *J. Org. Chem.* **1987**, *52*, 2083. (b) Hine, J.; Ahn, K. *J. Org. Chem.* **1987**, *52*, 2089.

[76] Kelly, T. R.; Meghani, P.; Ekkundi, V. S. *Tetrahedron Lett.* **1990**, *31*, 3381.

[77] (a) Etter, M. C.; Panunto, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5896. (b) Etter, M, C.; Urbañczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415.

[78] Curran, D. P.; Kuo, L. H. *J. Org. Chem.* **1994**, *59*, 3259.

[79] Curran, D. P.; Kuo, L. H. *Tetrahedron Lett.* **1995**, *36*, 6647.

[80] Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.

[81] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

[82] Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279.

[83] (a) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867. (b) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012.

[84] (a) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 15358. (b) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968.

[85] Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.

[86] Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102.

[87] Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem Commun.* **2006**, 1191.

[88] (a) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (b) Yamaoka, Y.; Miyabe, H.; Yasui, Y.; Takemoto, Y. *Synthesis* **2007**, 2571.

[89] Wang, Y.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156.

[90] Yamaoka, Y.; Miyabe, H.; Takemoto, Y. *J. Am. Chem. Soc.* **2007**, *129*, 6686.

[91] Jones, C. R.; Qureshi, M. K. N.; Truscott, f. R.; Hsu, S. T. D.; Morrison, A. J.; Smith, M. D. *Angew Chem. Int. Ed.* **2008**, *47*, 7099.

[92] Jones, C. R.; Pantoş, G. D.; Morrison, A. J.; Smith, M. D. *Angew. Chem. Int. Ed.* **2009**, *48*, 7391.

[93] Han, X.; Kwiatkowski, J.; Xue, F.; Huang, K.; Lu, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 7604.

[94] Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.

[95] Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151.

[96] Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713.

[97] (a) McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367. (b) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481.

[98] Wang, C.; Zhang, Z.; Dong, X.; Wu, X. *Chem. Commun.* **2008**, 1431.

[99] Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 6576.

[100] Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 16464.

[101] Mattson, A. E., Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932.

[102] Martin, N. J. A.; Ozores, L.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 8976.

[103] Martin, N. J. A.; Cheng, X.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 13862.

[104] (a) Schneider, J. F.; Falk, F.; Fröhlich, R.; Paradies, J. *Eur. J. Org. Chem.* **2010**, 2265. (b) Schneider, J. F.; Lauber, M. B.; Muhr, V.; Kratzer, D.; Paradies, J. *Org. Biomol. Chem.* **2011**, *9*, 4323.

[105] Dinér, P.; Nielsen, M.; Bertelsen, S.; Niess, B.; Jørgensen, K. A. *Chem. Commun.* **2007**, 3646.

[106] Uehara, H.; Barbas III, C. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 9848.

[107] For seminal work on Pd-catalysed C-N(sp^2) coupling, see: (a) Wolfe, J.; Åhman, J.; Sadighi, J.; Singer, R.; Buchwald, S. *Tetrahedron Lett.* **1997**, *38*, 6367. (b) Mann, G.; Hartwig, J. F.; Driver, M. S.; Rivas, C. F. *J. Am. Chem. Soc.* **1998**, *120*, 827.

[108] Lykke, L.; Monge, D.; Nielsen, M.; Jørgensen, K. A. *Chem. Eur. J.* **2010**, *16*, 13330.

[109] (a) Wyttenbach, T.; Liu, D.; Bowers, M. T. *Int. J. Mass. Spectrom.* **2004**, *231-239*, 221. (b) Kaiser, E. T.; Kézdy, F. J.; *Proc. Natl. Acad. Sci. USA* **1983**, *80*, 1137.

[110] Li, X.; Li, Y.; Peng, F.; Wu, S.; Li, Z.; Sun, Z.; Zhang, H.; shao, Z. *Org. Lett.* **2011**, *13*, 6160.

[111] Zhang, W.; Tan, D.; Lee, R.; Tong, G.; Chen, W.; Kuo-, B. Q.; Huang, W.; Tan, C.; Jiang, Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 10069.

[112] Singh, R. P.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2010**, *132*, 9558.

[113] See Burns, N. Z.; Witten, M. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 14578 and references therein.

[114] Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030.

[115] (a) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem. Int. Ed.* **2005**, *44*, 807. (b) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Müller, T. N.; Lex, J. *Chem. Commun.* **2005**, 1898.

[116] De, C. K.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 14538.

[117] (a) De, C. K.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 17060. (b) Klauber, E. G.; De, C. K.; Shah, T. K.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 13624. (c) Klauber, E. G.; Mittal, N.; Shah, T. K.; seidel, D. *Org. Lett.* **2011**, *13*, 2464.

[118] Stepney, G. PhD Thesis, *University of Nottingham*, **2008**.

[119] Czekelius, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 4793.

[120] Czekelius, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 4575.

[121] Czekelius, C.; Carreira, E. M. *Org. Process Res. Dev.* **2007**, *11*, 633.

[122] (a) Lam, H. W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225. (b) Chuzel, O.; Deschamp, J.; Chausteur, C.; Riant, O. *Org. Lett.* **2006**, *8*, 5943. (c) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem. Int. Ed.* **2006**, *45*, 1292. (d) Lipshutz, B. H.; Amorelli, B.; Unger, J. B. *J. Am. Chem. Soc.* **2008**, *130*, 14378.

[123] Du, Y.; Xu, L.; Shimizu, Y.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 16146.

[124] Chiu, P.; Chung, W. K. *Synlett* **2004**, 55.

[125] Peace, S. PhD Thesis, *University of Sheffield*, **1998**.

[126] Seebach, D.; Beck, A.K.; Mukhopadhyay, T.; Thomas, E. *Helv. Chim. Acta*. **1982**, *65*, 1101.

[127] Anderson, J. C.; Noble, A.; Tocher, D. A. *J. Org. Chem.* **2012**, *77*, 6703.

[128] Mitchell, J. M.; Finney, N. S. *Tetrahedron Lett.* **2000**, *41*, 8431.

[129] Khaksar, S.; Heydari, A.; Tajbakhsh, M.; Vahdat, S. M. *J. Fluorine Chem.* **2010**, 1377.

[130] Ouellet, S. G.; Walji, A. M.; Macmillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327.

[131] Tuttle, J. B. PhD Thesis, *California Institute of Technology*, **2008**.

[132] Ng, K.; Somanathan, R.; Walsh, P. J. *Tetrahedron Asymmetry* **2001**, *12*, 1719.

[133] Eliel, E. L.; Wilen, S. H.; Mander, L. N. in *Stereochemistry of Organic Compounds*, Wiley, New York, **1993**.

[134] Liu, X-.; Yan, Y.; Want, Y-.; Wang, C.; Sun, Jian. *Chem. Eur. J.* **2012**, *18*, 9204.

[135] Gust, R.; Gelbcke, M.; Angermaier, B.; Bachmann, H.; Krauser, R; Schoneneberger, H. *Inorg. Chim. Acta* **1997**, *264*, 145.

[136] Laurence, C.; Graton, J.; Berthelot, M.; Besseau, F.; Le Questel, J.; Luçon, M.; Ouvrard, C.; Planchat, A.; Renault, E. *J. Org. Chem.* **2010**, *75*, 4105.

[137] Le Questel, J.; Laurence, C.; Lachkar, A.; Helbert, M.; Berthelot, M. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2091.

[138] Chardin, A.; Laurence, C.; Berthelot, M.; Morris, D. G. *J. Chem. Soc., Perkin Trans. 2* **1996**, 1047.

[139] Laurence, C.; Berthelot, M.; Le Questel, J.; El Ghomeri, M. J. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2075.

[140] Taft, R. W.; Gurka, D.; Joris, L.; Schleyer, P. v. R.; Rakshys, J. W. *J. Am. Chem. Soc.* **1969**, *91*, 4801.

[141] Cacelli, I.; Campanile, S.; Giolitti, A.; Molin, D. *J. Chem. Inf. Model.* **2005**, *45*, 327.

[142] Alvarez-Casao, Y.; Marques-Lopez, E.; Herrara, R. P. *Symmetry* **2011**, *3*, 220.

[143] Kobayashi, J.; Cheng, J. F.; Ohta, T.; Nozoe, S.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem.* **1990**, *55*, 3666.

[144] Ito, T.; Kitajima, M.; Takayama, H. *Tetrahedron Lett.* **2009** *50*, 4506.

[145] Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796.

[146] Kuehne, M. E.; Muth, R. S. *J. Org. Chem.* **1991**, *56*, 2701.

[147] Nyerges, M.; Danscó, A.; Bitter, I.; Blaskó, G.; Tőke, L. *Tetrahedron Lett.* **2005**, *46*, 6927.

[148] Rey, A. W.; Szarek, W. A.; Maclean, D. B. *Can. J. Chem.* **1992**, *70*, 2922.

[149] Movassaghi, M.; Hill, M. D. *Org. Lett.* **2008**, *10*, 3485.

[150] Zheng, C.; You, S. *Chem. Soc. Rev.* **2012**, *41*, 2498.

[151] (a) Procuranti, B.; Connon, S. J. *Chem. Commun.* **2007**, 1421. (b) Chen, Q.; Chen, M.; Yu, C.; Shi, L.; Wang, D.; Yang, Y.; Zhou, Y. *J. Am. Chem. Soc.* **2011**, *133*, 16432.

[152] Satyanarayana, T.; Abraham, S.; Kagan, H. B. *Angew. Chem. Int. Ed.* **2009**, *48*, 456.

[153] Pelletier, J. C.; Cava, M. P. *J. Org. Chem.* **1987**, *52*, 616.

[154] Amarasinghe, N. R.; Turner, P.; Todd, M. H. *Adv. Synth. Catal.* **2012**, 2954.

[155] Perrin, D. D.; Armarego, L. F. in *Purification of Laboratory Compounds* 3rd Ed., Pergamon Press, New York, **1992**.

[156] Larrow, J. F.; Jacobsen, E. N. *Org. Synth.* **1998**, *75*, 1.

[157] Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1993**, *58*, 3850.

[158] Sader-Bakaouni, L.; Charton, O.; Kunesch, N.; Tillequin, F. *Tetrahedron* **1998**, *54*, 1773.

[159] McNamara, Y. M.; Keating, J. J.; Butler, S. G.; Meegan, M. J.; Cloonan, S. M.; Knox, A. J. S.; Williams, A. C.; Peters, G. H. *Bioorgan. Med. Chem.* **2011**, *19*, 1328.

[160] Cano, R.; Ramon, A. J.; Yus, M. *J. Org. Chem.* **2011**, *76*, 5547.

[161] Jarrahpour, A.; Zarei, M.; Fadavi, A. *Bull. Chem. Soc. Jpn.* **2011**, *84*, 320.

[162] Kumar, A.; Samuelson, A. G. *J. Organomet. Chem.* **2010**, 338.

[163] Ouali, A.; Spindler, J.; Jutand, A.; Taillefer, M. *Adv. Synth. Catal.* **2007**, 1906.

[164] Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Org. Chem.* **1994**, *59*, 1238.

[165] Barluenga, J.; Jimenez-Aquino, A.; Aznar, F.; Valdes, C. *J. Am. Chem. Soc.* **2009**, *131*, 4031.

[166] Vernall, A. J.; Ballet, S.; Abell, A. A. *Tetrahedron* **2008**, *64*, 3980.

[167] Andrés, J. M.; Manzano, R.; Pedrosa, R. *Chem. Eur. J.* **2008**, *14*, 5116.

[168] Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.

[169] Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964.

[170] O., M. Burak; Comeau, A. B.; Seto, C. T. *J. Org. Chem.* **2005**, *70*, 10792.

[171] Rasappan, R.; Rieser, O. *Eur. J. Org. Chem.* **2009**, 1305.

[172] Jiang, L.; Wu, T.; Chen, Y.; Zhu, J.; Deng, J. *Org. Biomol. Chem.* **2006**, *4*, 3319.

[173] Cortez, N. A.; Aguirre, G.; Parra-Hake, M.; Somanathan, R. *Tetrahedron Asymmetry* **2008**, *19*, 1304.

[174] Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 15872.

[175] Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, 779.

[176] Xue, D.; Chen Y-C.; Cui, X.; Wang, Q-W.; Zhu, J.; Deng, J-G. *J. Org. Chem.* **2005**, *70*, 3584.

[177] Xia, J.-J.; Wang, G.-U. *Synthesis* **2005**, 2379.

[178] Huyser, E. S.; Kahl, A. A. *J. Org. Chem.* **1970**, *35*, 3742.

[179] Roomi, M. W. *J. Med. Chem.* **1975,** *18*, 457.

[180] Nowrouzi, N.; Jonaghani, M. Z. *Can. J. Chem.* **2012**, *90*, 498.

[181] Wang, C.; Basca, J.; Xiao, J.; Pettman, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 7548.

[182] Gonzalez-Gomez, A.; Dominguez, G.; Perez-Castells, J. *Tetrahedron*, **2009**, *65*, 3378.

[183] White, J. D.; Li, Y.; Ihle, D. C. *J. Org. Chem.* **2010**, *75*, 3569.

[184] Delgado, R.; Blakey, S. B. *Eur. J. Org. Chem.* **2009**, *10*, 1506.

[185] Cole, D. C.; Stock, J. R.; Lennox, W. J.; Bernotas, R. C.; Ellingboe, J. W.; Boikess, S.; Coupet, J.; Smith, D. L.; Leung, L.; Zhang, G.-M.; Feng, X.; Kelly, M. F.; Galante, R.; Huang, P.; Dawson, L. A.; Marquis, K.; Rosenzweig-Lipson, S.; Beyer, C. E.; Schecter, L. E. *J. Med. Chem.* **2007**, *50*, 5535.